Title: A Phase 2, Randomized, Controlled, Open-Label, Clinical Study of the Efficacy and Safety of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine in Patients with Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Low-Blast Acute Myelogenous Leukemia

NCT Number: NCT02610777

SAP Approve Date: 06 August 2019

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Pevonedistat-2001

A Phase 2, Randomized, Controlled, Open-Label, Clinical Study of the Efficacy and Safety of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine in Patients with Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Low-Blast Acute Myelogenous Leukemia

PHASE 2

Version**: Amendment 01**

Date**:** 06 August 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 04

Protocol Date: 27 July 2018

1.1 Approval Signatures

Study Title: A Phase 2, Randomized, Controlled, Open-Label, Clinical Study of the Efficacy and Safety of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Low-Blast Acute Myelogenous Leukemia

PPD

Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AML	acute myelogenous leukemia
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CMML	chronic myelomonocytic leukemia
CR	complete remission
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
ELN	European LeukemiaNet
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment (visit)
EQ-5D	EuroQol 5-Dimensional Health Questionnaire
FA	final analysis
HRMDS	higher-risk myelodysplastic syndromes
HU	health utilization
IA	interim analysis
IB	Investigator's Brochure
IDMC	independent data monitoring committee
IPSS-R	Revised International Prognostic Scoring System
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PK	pharmacokinetic(s)
PR	partial remission

Abbreviation	Term
PRO	patient-reported outcome
PSMB1	Proteasome subunit beta type-1
QLQ	Quality of Life Questionnaire (EORTC)
Abbreviation	Term
QTc	rate-corrected QT interval (millisec) of electrocardiograph
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SD	stable disease
SMQs	Standardised MedDRA Queries
SQ	Subcutaneous
TEAE	treatment-emergent adverse event
US	United States
WBC	white blood cell
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives are:

- To determine in patients with HR MDS or CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves overall survival (OS) when compared with single-agent azacitidine.

4.2 Secondary Objectives

The secondary objectives are:

- To determine in patients with HR MDS or CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves event-free survival (EFS) when compared with single-agent azacitidine; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death.
- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine improves 6-month and 1-year survival rates when compared with single-agent azacitidine.
- To determine in patients with HR MDS or CMML whether the combination of pevonedistat and azacitidine delays time to AML transformation when compared with single-agent azacitidine.
- To determine in patients with HR MDS or CMML, and low-blast AML whether the combination of pevonedistat and azacitidine, when compared to single-agent azacitidine, improves the rate of complete remission (CR) (composite CR [CR+ CRi] in patients with low-blast AML), CR plus partial remission ((composite CR + PR for patients with low-blast AML), overall response, and/or CR (not including CRi) in low-blast AML. Overall response in HR MDS or CMML is defined as CR+PR+hematologic improvement [HI]; overall response in low-blast AML is defined as CR+CRi +PR.
- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves the rate of CR (composite CR [CR+ CRi] in patients with low-blast AML), CR + PR (composite CR + PR in patients with low-blast AML), overall response, as well as CR (not including CRi) in low-blast AML by Cycle 4.
- To determine in patients with HR MDS or CMML, and low-blast AML whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves duration of CR (composite CR [CR+ CRi] in patients with low-blast AML), CR + PR (composite CR + PR in patients with low-blast AML), overall response, and/or CR (not including CRi) in patients with low-blast AML.

- To determine in patients with HR MDS or CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves time to first CR (CR for HR MDS/CMML and low-blast AML; CR + CRi [composite CR] for low-blast AML), or PR when compared with single-agent azacitidine.
- To determine in patients with HR MDS or CMML, and low-blast AML whether the combination of pevonedistat and azacitidine delays time to subsequent therapy when compared with single-agent azacitidine. Subsequent therapy is defined as agent(s) with antileukemic/anti-MDS activity (eg, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.
- To determine in patients with HR MDS or CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves rate of transfusion independence when compared with single-agent azacitidine. RBC or platelet transfusion independence requires that the patient, receive no RBC or platelet transfusions, respectively, for a period of at least 8 weeks.
- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine reduces the percent of patients who have at least one inpatient hospital admission(s) related to HR MDS or CMML, or low-blast AML when compared with single-agent azacitidine.
- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine delays time to PD, relapse after CR or PR (HR MDS/CMML) or CR (low-blast AML), or death when compared to single-agent azacitidine.
- To evaluate in patients with HR MDS or CMML and low-blast AML, the safety of the combination of pevonedistat and azacitidine when compared with single-agent azacitidine.
- To collect in patients with HR MDS or CMML, and low-blast AML, plasma concentration-time data for pevonedistat to contribute to future population PK analyses of pevonedistat.

4.3 Exploratory Objectives

CCI

[redacted]

CCI

4.4 Study Design

This study is a multicenter, global, randomized, controlled, open-label, phase 2 clinical study of the combination of pevonedistat and azacitidine versus single-agent azacytidine administered in patients with HR MDS or CMML and low-blast AML who have not previously received a hypomethylating agent. Patients with nonproliferative CMML (ie, white blood cell [WBC] <20,000/μL) are included because these patients were also included in both randomized studies of azacitidine conducted in the US and the European Union with similar response rates to patients with MDS.

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

It is expected that approximately 117 patients will be enrolled in this study. Once enrolled, patients (MDS, CMML, and low-blast AML) will be randomized at a 1:1 ratio to receive study drug (either single-agent azacitidine or the combination of pevonedistat and azacitidine) in 28-day treatment cycles. All patients will be stratified into 4 categories: low-blast AML, IPSS-R risk groups of very high, high, or intermediate for MDS/CMML. Note that patients with HR MDS/CMML with indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points, ie, intermediate, for determining overall Prognostic

Risk Category/Score. All patients will receive azacitidine (75 mg/m^2 [IV or SC]) on Days 1 through 5, Day 8, and Day 9. Patients randomized to the combination arm will also receive pevonedistat (20 mg/m^2 via 60 ([±10]-minute infusion) on Days 1, 3, and 5. Modifications to the dose and schedule may be allowed as detailed in the Schedule of Events.

Patients, including those who achieve a CR, may receive study treatment until they experience unacceptable toxicity, relapse, transformation to AML, or PD. Patients with HR MDS or CMML may be allowed to continue study treatment (either treatment arm) if they meet the criteria for progressive disease based only on bone marrow blast count (without AML transformation) if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients with low-blast AML in this study may also be allowed to continue study treatment (either treatment arm), even if they meet the criteria for progressive disease based only on bone marrow blast counts, if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment. Patients may choose to discontinue therapy at any time.

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. After the EOT visit, patients will enter EFS follow-up (for patients with HR MDS or CMML) or response follow-up (for patients with low-blast AML), with study visits every 3 months, to include physical exam, clinical blood tests, HRQOL assessments, hospitalization assessment, bone marrow aspirate sampling, and disease assessment, if their disease has not transformed to AML (for patients with HR MDS or CMML) or progressed (for patients with low-blast AML), and they have not started subsequent therapy. Patients will enter OS follow-up (contacted every 3 months to document subsequent therapies and survival status) when they have confirmed transformation to AML (for patients with HR MDS or CMML) or experienced progressive disease (for patients with low-blast AML) or have started subsequent therapy.

Disease response assessments for all patients with HR MDS or CMML will be based on the Modified International Working Group (IWG) response criteria for MDS. Disease response assessments for patients with low-blast AML will be based on the Revised Recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Formal disease assessments for study endpoints will be determined based on local bone marrow aspirate blast counts and transfusions, and central lab data (local lab data may be used for time-sensitive clinical decisions).

Inpatient hospital admissions related to HR MDS or CMML or low-blast AML, as well as transfusion independence, will be monitored as secondary efficacy endpoints. RBC- and platelet-transfusion independence requires that the patient receive no RBC or platelet transfusions, respectively, for a period of at least 8 weeks. Treatment-emergent resistance will also be monitored.

A bone marrow aspirate and biopsy will be collected at Screening, and bone marrow aspirates will be collected during treatment and follow-up for blast count evaluation (to inform disease burden assessment). Bone marrow aspirates obtained at time points described in the Bone Marrow Collection and Assessment Schedule will also be used CCI [redacted]

Sparse sampling for the determination of pevonedistat plasma concentrations and, if appropriate, its metabolites will be collected from each patient in the Combination Pevonedistat Plus Azacitidine Arm to contribute to a population PK analysis of pevonedistat co-administered with azacitidine.

Adverse events and ECOG performance status will be assessed, and ECGs, clinical laboratory values, and vital signs 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 4.03, effective date 14 June 2010. Dose modification guidelines are presented in Section 6.3 in the protocol.

CCI [redacted]

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

OS is the primary endpoint.

5.1.2 Secondary Endpoint

The secondary endpoints are:

- EFS: for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death.
- Six-month and 1-year survival rates.
  - Time to AML transformation in patients with HR MDS or CMML.
- CR (CR for HR MDS and CMML; CR + CRi [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) + PR, overall response (CR + PR + HI for HR MDS and CMML; CR + CRi + PR for low-blast AML), CR (not including CRi) in low-blast AML.
- CR (CR for HR MDS and CMML; CR + CRi [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) + PR, overall response (CR + PR + HI for HR MDS and CMML; CR + CRi + PR for low-blast AML) by Cycle 4, CR (not including CRi) in low-blast AML by Cycle 4.
- Duration of CR (CR for HR MDS and CMML, CR + CRi [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) + PR, overall response (CR + PR + HI for HR MDS and CMML; CR + CRi + PR for low-blast AML), and duration of CR (not including CRi) in low-blast AML.
- Time to first CR (CR for HR MDS/CMML and low-blast AML; CR + CRi [composite CR] for low-blast AML) or PR for HR MDS/CMML and low-blast AML.
- Time to subsequent therapy.
- RBCs and platelet-transfusion independence.
- Percentage of patients with at least 1 inpatient hospital admissions related to HR MDS or CMML (collected through transformation to AML or until initiation of subsequent therapy, whichever occurs first) or low-blast AML (collected through AML progression or until initiation of subsequent therapy, whichever occurs first).
- Time to PD, relapse, or death.
- AEs and serious adverse events (SAEs), abnormal clinical laboratory values, Eastern Cooperative Oncology Group (ECOG) performance status, ECGs, and vital sign measurements.

5.1.3 Exploratory Endpoints

CCI

6.0 DETERMINATION OF SAMPLE SIZE

Approximately 117 patients will be randomized in a 1:1 ratio to receive either the combination of pevonedistat and azacitidine or single-agent azacitidine.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage (of nonmissing) per category for categorical data, unless specified otherwise.

7.1.1 Blinding and Unblinding

This is an open-label study; investigators and patients will know the individual treatment assignments.

7.1.2 Randomization and Stratification

The randomization scheme will be generated by an independent statistician at Millennium who is not on the study team. Before dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an interactive web-based response system (IWRS).

Patients will be randomized to receive the combination of pevonedistat and azacitidine or azacitidine alone in a 1:1 ratio, stratified into 4 categories: low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML [1]. (CCI [redacted]

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 based on the scheduled visit at which they were 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 dates in Adverse Event

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.

a) 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.

7.1.7 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 will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

The ITT population will be used for the primary and secondary efficacy analyses, and resource utilization and patient-reported outcome analysis.

7.2.2 Safety Population

The safety population is defined as all patients who receive at least 1 dose of pevonedistat plus azacitidine or azacitidine alone. Patients will be analyzed according to the actual treatment they received. That is, those patients who are randomized to Arm B but received the regimen in Arm A will be included in Arm A; those patients who are randomized to Arm A but received the regimen in Arm B will be included in Arm B for safety analyses. Patients who received any dose of pevonedistat will be included in the combination pevonedistat plus azacitidine arm, and patients who did not receive any dose of pevonedistat and received at least 1 dose of azacitidine will be included in the single-agent azacitidine arm, regardless of their randomized treatment.

The safety population will be used for all safety-related analyses such as AEs, concomitant medications, laboratory tests, and vital signs.

7.2.3 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 baseline, and at least 1 postbaseline disease assessment.

The response evaluable population will be used for the analyses of response rates, and time to response. The response-evaluable patients must have disease assessment at baseline, which is defined by:

- CCI [redacted]

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 or the subset of patients with HR MDS/CMML, HR MDS and CMML separately.

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

Disposition will be generated for the ITT population, patients with HR MDS/CMML, HR MDS and CMML separately.

A listing will present data concerning patient disposition.

The stratification strata at randomization is based on the disease diagnose at screening, for the patients whose disease diagnose were 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 the ITT population, patients with HR MDS/CMML, patients with HR MDS and CMMLseparately. Baseline demograph ic 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 baseline. If a weight at Cycle 1 Day 1 pre-dose is not available, the screening weight 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 for the ITT patients, patients with HR MDS/CMML, and patients with HR MDS separately. 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

Analysis on baseline disease characteristics will be performed for the ITT patients, patients with HR MDS/CMML, and patients with HR MDS separately.

Baseline disease characteristics (HR MDS/CMML, HR MDS, CMML : disease type of de novo or secondary, disease subtype if secondary, French-American-British (FAB) category, WHO classification of tumors, Modified Charlson Comorbidity Index, and IPSS-R category; low-blast AML: disease type of de novo or secondary, disease subtype if secondary, revised WHO classification of AML, evidence of extramedullary disease; HR MDS/CMML, HR MDS, CMML, AML: 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.

HR MDS/CMML patients, HR MDS patients, CMML patients will be classified into 3 categories based on the IPSS-R score: intermediate, high, very high.

Separate tables for HR MDS/CMML patients, HR MDS patients, CMML patients and low-blast AML patients 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 transplant (including type of procedure and months from last procedure to first dose of pevonedistat) 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 will also be summarized.

CCI

[redacted]

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 all patients.

7.6 Medication History

General medical history and prior medications will be listed for the ITT patients, patients with HR MDS/CMML and HR MDS separately.

7.7 Concomitant Medications

Analysis on concomitant medications will be performed for the ITT patients, patients with HR MDS/CMML, and patients with HR MDS separately.

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.

7.8 Study Drug Exposure and Compliance

Analysis on extent of exposure will be performed for the ITT patient, patients with HR MDS/CMML, and patients with HR MDS separately.

7.8.1 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 plus 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 plus azacitidine in the safety population.

Dosing intensity will be summarized for the treatment arm of pevonedistat plus 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. Body surface area (BSA) will be calculated on Cycle 1, Day 1, and at subsequent visits if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

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

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

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

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

Total dose expected will be calculated based on the BSA measured at baseline. 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 plus 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:

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

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

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

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

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

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

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

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.

7.8.2 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.

Analysis on treatment compliance and modifications will be performed for the ITT patients, patients with HR MDS/CMML, and patients with HR MDS separately.

7.8.3 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 die, 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).

Analysis on duration of follow-up will be performed for the ITT population, patients with HR MDS/CMML, and patients with HR MDS separately.

7.9 Efficacy Analysis

All efficacy evaluations will be conducted for the ITT patients, patients with HR MDS/CMML, and patients with HR MDS separately. Analyses based on other subsets of patients will be specified when needed.

7.9.1 Primary Efficacy Endpoints

OS is the primary endpoint. Analysis on OS will be presented for ITT patients, HR MDS/CMML patients, HR MDS patients and CMML patients separately. OS also will be assessed separately in patients with LB AML.

Primary Analysis

OS will be analyzed and tested at the final analysis when approximately 60% of patients with HR MDS/CMML have experienced OS events, or termination of the study by the sponsor.

CCI

[redacted]

OS will be calculated from 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. Unstratified log-rank test will be used to compare OS between the 2 treatment arms. Hazard ratios, along with the 2-sided 95% CIs will be estimated using the unadjusted unstratified Cox models. Kaplan-Meier curves, Kaplan-Meier medians (if estimable), and survival probability at 6 months and 1 year, together with the 95% CIs, will be calculated for each treatment group.

In addition, an unstratified 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: age (<65, 65-74, >=75), de novo versus secondary, disease risk group (IPSS-R risk categories for HR MDS/CMML: very high, high, intermediate; CCI [redacted] Additional exploratory analyses may be performed if deemed necessary.

Sensitivity Analysis

To adjust for the potential confounding effects of post-treatment transplantation after patients discontinued study treatment, unstratified log-rank tests and unstratified Cox model will be applied to OS with censoring at the start of post-treatment transplantation.

To adjust for the potential confounding effects of subsequent therapies after patients discontinue study treatment, the following 2 methods will be used:

1. Marginal Structural Models (MSMs) by Robins et al., 2000.
2. Inverse Probability of Censoring Weighted (IPCW) method by Robins and Finkelstein, 2009.

In the MSM and IPCW analyses, in order to derive weights adjusting for the time-fixed and time-varying confounding effects due to taking alternative therapies, the covariates that affect disease progression and post-progression treatment, and the OS endpoint will be used. Baseline covariates include region (North America (NA) vs ex NA), age (< 65 years, >=65 and <= 74 years, >= 75 years), race (white, non-white), ECOG score (0 or 1, 2), disease type (de novo or secondary, baseline peripheral WBC, baseline platelets, disease risk group (for AML, ELN 2017, adverse, intermediate, favorable, for HR MDS/CMML, IPSS-R, very high, high, intermediate). Time-varying covariates include duration of treatment exposure, disease progression status at each study visit, RBC Transfusion at each study visit, platelet transfusion at each study visit, indication of subsequent therapy (yes or no), additional therapy with transplantation. The final criteria for selected covariates would need to be statistically have a p-value of less than or equal to 0.1 in the multivariate Cox regression models for weight calculations, and in the final Cox model for OS. If there are more than 5% missing in the covariate, then this covariate will be dropped from the weighting calculation and final OS model. For both MSM and IPCW analyses, logistic regression models on repeated measurements will be used to approximate the Cox models in the weight derivations from which stabilized weights will be derived per subject per observation. Adjusted K-M curves will also be presented along with hazard ratios (HRs), 95% confidence intervals for HRs, and adjusted p-values based on MSM and IPCW approaches. SAS proc PHREG procedure with counting process type of data input, which takes multiple observations per subject, will be used as the final Cox model for OS for both MSM and IPCW approaches.

Subgroup Analysis

Subgroup analyses will be performed for OS relative to baseline stratification factors, demographic data such as sex, race, and age, and disease characteristics such as de novo or secondary. The subgroup analysis for OS will be presented for ITT patients, HR MDS/CMML patients, HR MDS patients and CMML patients separately.

The statistical model will be adjusted accordingly to fit the subgroup analyses. The details on subgroups are presented in the following:

Table 7.a List of Subgroups

Subgroup	Definition of Group
Age	< 65 years, ≥65 and ≤ 74 years, ≥75 years
Sex	male vs female
Region	North America (NA) vs ex NA
IPSS-R risk category & low-blast AML	very high, high, intermediate, or low-blast AML
Indication	HR MDS/CMML, HR MDS, CMML, or low-blast AML
Low-blast AML ELN risk	adverse, intermediate and favorable
ECOG performance status	0 or 1 vs 2
Disease type	de novo, secondary
peripheral WBC	<15,000 per μL vs ≥15,000 per μL
Platelet	<100,000 vs ≥100,000 per μL

7.9.2 Secondary Efficacy Endpoint

Event-Free Survival (EFS)

EFS event is defined as death or transformation to AML for HR MDS/CMML patients, whichever occurs first, or defined as death for low-blast AML patients. EFS is defined as the time from the date of randomization to the date of the occurrence of an event.

Transformation to AML for HR MDS/CMML patients is defined according to WHO Classification [1].

For HR MDS/CMML patients, patients without documentation of transformation to AML will be censored at the date of the last response assessment. Stem cell transplantation (SCT) is not considered as alternate antineoplastic therapy. Following Cycle 4, bone marrow disease assessment will be performed only as clinically indicated at the suspicion of relapse in patients with HR MDS/CMML who achieve CR. Bone marrow disease assessment is not required to be regularly assessed after Cycle 4 for patients with HR MDS/CMML who achieve CR. Therefore, EFS event after more than 3 cycles or equivalent from the last disease assessment which is Cycle 4 or beyond for patients with HR MDS/CMML who achieve CR is considered as an event. HR MDS/CMML patients with no response assessment will be censored at the date of randomization.

For low-blast AML patients, patients without documentation of death will be censored at the date that the patient was last known to be alive.

The details regarding the handling of missing assessments and censoring for HR MDS/CMML patients for the EFS key analysis are based on the FDA rules and presented in Table 7.b.

Table 7.b Handling of Missing Assessments and Censoring for HR MDS/CMML Patients for EFS Key Analysis Based on The FDA Rules

Situation	Date of Event or Censoring	Outcome
No baseline and/or no post baseline assessment, no subsequent anticancer therapy after study treatment, no death	Date of Randomization	Censored
Transformation to AML documented between scheduled visits	Date of documented transformation to AML	Event
No documented EFS event	Date of last adequate assessment[a]	Censored
Lost to follow-up, withdraw consent before any documented EFS event	Date of last adequate assessment[a]	Censored
EFS event after more than 1 missed visit (excluding HR MDS/CMML patients who achieve CR and last disease assessment is Cycle 4 or beyond prior to the EFS event)	Date of last adequate assessment[a]	Censored
EFS event after more than 1 missed visit from the last disease assessment which is Cycle 4 or beyond for HR MDS/CMML patients who achieve CR	Date of documented EFS event	Event
Alternate antineoplastic therapy started prior to transformation to AML (excluding stem cell transplantation)	Date of last adequate assessment prior to starting alternate antineoplastic therapy	Censored
Death before first assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event

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

Key Analysis

Key analysis on EFS will be performed for the ITT patient, patients with HR MDS/CMML, patients with HR MDS and patients with CMML separately.

Unstratified log-rank test will be used to compare EFS between the 2 treatment arms.

Unstratified Cox models will be used to estimate the hazard ratio and its 2-sided 95% CIs for the treatment effect. The Kaplan Meier (K-M) survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment arm.

In addition, an unstratified 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: age (<65, 65-74, ≥75), de novo versus secondary, disease risk group (IPSS-R risk categories for HR MDS/CMML: very high, high, intermediate; ELN 2017 cytogenetic risk categories for low-blast AML: adverse, intermediate, favorable), region (North America vs ex North America), baseline ECOG score

(0-1 vs 2), baseline peripheral WBC (<15,000 per µL vs ≥15,000 per µL), baseline platelet (<100,000 vs ≥100,000 per µL). Additional exploratory analyses may be performed if deemed necessary.

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.

The proportional hazard assumptions will be examined and sensitivity analysis will be conducted if appropriate.

Subgroup analyses will be performed using subgroups defined for OS analyses.

Sensitivity Analysis

EFS using different censoring mechanisms for patients with HR MDS/CMML will be analyzed, for example, not censoring for patients who discontinue treatment and go on alternative antineoplastic therapy. The details of the handling of missing assessments and censoring for patients with HR MDS/CMML based on the EMA rules for sensitivity analyses are presented in Table 7.c. Sensitivity analyses for EFS based on the EMA rules will be performed based on the alterations of the handling of missing assessment and censoring in Table 7.c, on the basis of combined alterations, as well as 1 alteration at a time.

Table 7.c Handling of Missing Assessments and Censoring for HR MDS/CMML Patients for EFS Sensitivity Analysis Based on The EMA Rules

Situation	Date of Event or Censoring	Outcome
Alternate antineoplastic therapy started prior to transformation to AML	Date of documented transformation to AML	Event
EFS event after more than one missed visit	Date of documented EFS event	Event

Additional sensitivity analyses for EFS using other censoring mechanisms for patients with HR MDS/CMML include:

- SCT is considered as alternate antineoplastic therapy for patients with HR MDS/CMML, and patients with HR MDS/CMML who have SCT prior to transformation to AML will be censored at the date of last adequate assessment prior to starting SCT.
- If HR MDS/CMML patients who achieve CR have EFS event after more than 1 missed visit from the last disease assessment which is Cycle 4 or beyond, these patients will be censored at the date of last adequate disease assessment.
- Combine the above 2 scenarios: (1) SCT is considered as alternate antineoplastic therapy for patients with HR MDS/CMML, and patients with HR MDS/CMML who have SCT prior to transformation to AML will be censored at the date of last adequate assessment prior to starting SCT; (2) If HR MDS/CMML patients who achieve CR have EFS event after more than 1 missed visit from the last disease assessment which is Cycle 4 or beyond, these patients will be censored at the date of last adequate disease assessment.

- If there is no documented EFS events, HR MDS/CMML patients with CR will be censored at the date of the last visit with hematological evaluation, or the date of last bone marrow disease assessment, whichever occurs later.

Six-Month and One-Year Survival Rate

Kaplan-Meier estimates and the 95% CIs of 6-month and 1-year survival rates will be provided by treatment arm based on the ITT population, patients with HR MDS/CMML, and patients with HR MDS.

Time to AML Transformation

Time to AML transformation is defined as time from randomization to documented AML transformation. This definition only applies to HR MDS and CMML patients, so this analysis will only be carried out in this subgroup of the ITT population and separately for HR MDS patients and CMML patients. Patients who died before progression to AML will be censored at the date of death. Patients without documented AML transformation at the time of the analysis will be censored at the date of the last assessment. Time to AML transformation is a time-to-event variable, which will be analyzed using a similar method as OS.

CR (CR for HR MDS and CMML, CR + CRi [composite CR] for low-blast AML)/CR (CR for HR MDS and CMML, CR + CRi for low-blast AML)+PR/Overall Response (CR+PR+HI for HR MDS and CMML; CR+CRi+PR for low-blast AML)/ CR (not including CRi) in low-blast AML

Rate of CR/CR+PR (composite CR + PR for patients with low-blast AML)/overall response /CR (not including CRi) in low-blast AML respectively, are defined as the proportion of patients who achieve CR/PR or better /overall response/ CR (not including CRi) in low-blast AML. Overall response is defined as HI or PR or better for HR MDS/CMML patients, and PR or better for low-blast AML patients. For low-blast AML patients, composite CR includes both complete remission (CR) and complete remission with incomplete count recovery (CRi).

The number and percentage of patients who achieved CR/CR+PR/overall response/CR (not including CRi) in low-blast AML, respectively, will be summarized by treatment group. CR rate/CR+PR rate/overall response rate/CR (not including CRi) rate in low-blast AML, respectively, will be tested using the unstratified Cochran-Mantel-Haenszel (CMH) chi-square test. The CMH chi-square test p-value, the relative risk with its 2-sided 95% CIs will be calculated. The absolute rate difference will be provided with its 95% CIs.

The key analysis will be based on the ITT population, patients with HR MDS/CMML, patients with HR MDS and patients with CMML separately, with response non-evaluable patients treated as non-responders. Sensitivity analysis will be performed using the response-evaluable population and response-evaluable patients with HR MDS/CMML and HR MDS separately.

CR (CR for HR MDS and CMML, CR + CRi [composite CR] for low-blast AML)/CR (CR for HR MDS and CMML, CR + CRi for low-blast AML) +PR/Overall Response (CR+PR+HI for HR MDS and CMML; CR+CRi+PR for low-blast AML)/ CR (not including CRi) in low-blast AMLby Cycle 4

Rate of CR/CR+PR/overall response/CR (not including CRi) in low-blast AML by cycle 4, respectively, are defined as the proportion of patients who achieve CR/PR or better / overall response/CR (not including CRi) in low-blast AML, respectively, by cycle 4.

The number and percentage of patients who achieved CR/CR+PR/overall response/CR (not including CRi) in low-blast AML by Cycle 4, respectively, will be summarized by treatment group. CR rate/CR+PR rate/overall response rate/ CR (not including CRi) rate in low-blast AML by cycle 4 are binary outcome variables, which will be analyzed similarly as CR rate/CR+PR rate/overall response rate/CR (not including CRi) rate in low-blast AML.

The key analysis will be based on the ITT population, patients with HR MDS/CMML, and patients with HR MDS separately, with response non-evaluable patients treated as non-responders. Sensitivity analysis will be performed using the response-evaluable population, response-evaluable patients with HR MDS/CMML and HR MDS separately.

MDS and CMML, CR + CRi [composite CR] for low-blast AML)/CR (CR for HR MDS and CMML, CR + CRi for low-blast AML) +PR/Overall Response (CR+PR+HI for HR MDS and CMML; CR+CRi+PR for low-blast AML)/ CR (not including CRi) in low-blast AML

Duration of CR/CR+PR/overall response/CR (not including CRi) rate in low-blast AML, respectively, is defined as the time from the date of first documentation of a CR/PR or better/ overall response/CR (not including CRi) rate in low-blast AML, respectively, to the date of first documentation of PD (HR MDS/CMML, low-blast AML), relapse from CR or PR (HR MDS/CMML), or relapse from CR (low-blast AML), whichever comes first, for responders of CR/PR or better/ overall response/CR (not including CRi) rate in low-blast AML, respectively. Responders without documentation of PD or relapse from CR (low-blast AML), or relapse from CR or PR (HR MDS/CMML) will be censored as below:

- key analysis: censored at the date of the last visit with hematological evaluation, or the date of last bone marrow disease assessment that is SD or better, whichever occurs later.
- sensitivity analysis: censored at the date of the last response assessment that is SD or better.

Duration of CR/CR+PR/overall response/CR (not including CRi) rate in low-blast AML will be summarized descriptively using the K-M method and separately for the overall responders, responders of HR MDS/CMML, responders of HR MDS, responders of CMML, responders of low-blast AML. Kaplan Meier (K-M) survival curves and K-M medians (if estimable) will be provided for each treatment arm.

Time to First CR or PR

Time to first CR (CR and composite CR for patients with low-blast AML) or PR is defined as the time from the date of randomization to the first documentation of PR or better. Patients who do

not develop any CR or PR will be censored at the date of their last disease assessment. Time to first CR or PR is a time-to-event variable, which will be analyzed based on the response-evaluable population and response-evaluable patients with HR MDS/CMML, HR MDS, CMML and AML separately, using a similar method as OS.

Time to Subsequent Therapy

Time to subsequent therapy is defined as the time from the date of randomization to the date of the first documented subsequent therapy (excluding stem cell transplantation). Subsequent therapy is defined as agent(s) with antileukemic/anti-MDS activity (eg, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy. Patients who do not receive subsequent therapy at the time of the analysis will be censored at the date of death or last contact. Time to subsequent therapy is a time-to-event variable, which will be analyzed based on the ITT population, patients with HR MDS/CMML, and patients with HR MDS separately, using a similar method as OS.

Rate of Transfusion Independence

A patient is defined as RBC or platelet-transfusion independent if he/she receives no RBC or platelet transfusions for a period of at least 8 weeks [4,5] during the time period from randomization through 30 days after the last dose of any study drug. Rate of transfusion independence is defined as the number of patients who become transfusion independent divided by the number of patients who are transfusion dependent at Baseline (ie, patients received RBC or platelet transfusion within 8 weeks before randomization). The number of patients who are transfusion dependent/independent at Baseline and post Baseline, as well as rate of transfusion independence, will be summarized by treatment group. Rate of transfusion independence will be tested using unstratified CMH test. P values and 2-sided 95% CIs of the relative risk will be provided. The absolute rate difference will be provided with its 95% CIs.

Analysis of rate of transfusion independence will be performed for the ITT patients, patients with HR MDS/CMML, and patients with HR MDS separately.

Percent of Inpatient Hospitalizations Related to HR MDS, CMML, or AML

Inpatient hospital admission data will be collected through transformation to AML (HR MDS/CMML patients) or disease progression (low-blast AML patients) or until initiation of subsequent therapy (all patients), whichever occurs first. The analysis will be based on the ITT population.

The number and percentage of patients who have any hospitalizations related to HR MDS, CMML, or AML will be summarized by treatment group. The absolute rate difference will be provided with its 95% CI.

Analysis will be performed for the ITT patients, patients with HR MDS/CMML, and patients with HR MDS separately.

Time to PD, Relapse After CR or PR (HR MDS/CMML), Relapse After CR (LB AML), or Death

Time to PD, relapse after CR or PR, relapse from CR, or death is defined as the time from the date of randomization until the date of the first documentation of disease progression, or relapse after CR or PR, or relapse from CR, or death due to any cause. Time to PD, relapse after CR or PR, relapse from CR, or death is a time-to-event variable, which will be analyzed based on the ITT population, patients with HR MDS/CMML, and patients with HR MDS separately, using a similar method as OS.

7.9.3 Additional Efficacy Endpoint(s)

Transfusion Independence

KM figure and table will be provided for the longest duration of transfusion independence for ITT patients, patients with HR MDS/CMML, and patients with HR MDS separately.

The transfusion rate per month (ie, number of transfusion received divided by the time [in month unit] from randomization through 30 days after the last dose of study dug) will also be summarized for both RBC and platelet separately.

Duration of HI

Table and figure will be provided for duration of HI, duration of HI-Neutrophil, duration of HI-Erythroid, duration of HI-Platelet for HR MDS/CMML and HR MDS population separately.

Allogeneic Stem Cell Transplantation

Rate of overall response and Allogeneic Stem Cell Transplantation will be summarized for ITT, HR MDS/CMML, HR MDS, CMML, low-blast AML.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis

Pevonedistat plasma concentration-time data will be presented in listings. Pharmacokinetic data will be used to perform future population PK analyses of pevonedistat using a nonlinear mixed effects modeling approach and to assess the effect of various covariates on pevonedistat PK. These analyses may additionally include data collected in other pevonedistat clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

7.10.2 Pharmacodynamic Analysis

Not applicable.

7.11 Other Outcomes

Not applicable.

7.11.1 Patient-Reported Outcomes (PROs)

Patient reported outcome assessments using the EORTC-QLQ-C30 and the QOL-E will be analysed using patients with PRO measurements at baseline and at least one post baseline measurement in the ITT population. For QOL-E data, the American English-speaking US patient population only will be used for analysis.

The descriptive statistics of actual values and changes from baseline of the subscale scores for the EORTC QLQ-C30 and QOL-E will be summarized by treatment arm over time in a table and accompanying sets of figures. The descriptive analyses will be conducted in the full population, the population of HR MDS/CMML patients, HR MDS patients, and the population of low blast AML patients. Additionally, the descriptive statistics of actual values and changes from baseline of global health status/quality of life (QOL) will be summarized by treatment arm over time by clinical response (responders and nonresponders). Responders are HR MDS/CMML patients who achieve HI, PR, or CR, or low-blast AML patients who achieve PR, CRi or CR. The subscales of the EORTC QLQ-C30 are defined in Table 7.d. The summary score of EORTC QLQ-C30 will be calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Health Status/QoL scale and the Financial Difficulties scale are not included). The subscales of the QOL-E are defined as in Table 7.e.

Table 7.d Description of EORTC QLQ-C30 domain scores

Subscale	Individual Items
Physical functioning	1-5
Role functioning	6-7
Emotional functioning	21-24
Cognitive functioning	20, 25
Social functioning	26-27
Quality of life	29- 30
Fatigue	10, 12, 18
Nausea and vomiting	14-15
Pain	9, 19
Dyspnea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial difficulties	28

Table 7.e Description of Subscale Scores of QOL-E

Subscale	Individual Items
Physical (QOL-FIS)	3a, 3b, 3c, 3d
Functional (QOL-FUN)	4a, 4b, 5
Social (QOL-SOC)	6a, 6b, 6c, 7
Sexual (QOL-SES)	8, 14f
Fatigue (QOL-FAT)	9, 10, 11a, 11b, 11c, 11d, 12
MDS-Specific (QOL-SPEC)	13, 14a, 14b, 14c, 14d, 14e, 14g
General (QOL-GEN)	QOL-FIS, QOL-FUN, QOL-SOC, QOL-SES, QOL-FAT
ALL	QOL-FIS, QOL-FUN, QOL-SOC, QOL-SES, QOL-FAT, QOL-SPEC
Treatment-outcome index (TOI)	QOL-FIS, QOL-FUN, QOL-SPEC

The number and percentage of patients with a change in EORTC QLQ C30 subscale scores from baseline achieving the published minimally important difference (MID) of 10 points will be summarized by treatment group over time in a table and figure. Specifically, patients with a change in score from baseline ≥MID in a direction reflecting deteriorating functioning or increased symptoms at a given time point will be classified as "worsened", whereas those with a change in score from baseline ≥MID in a direction reflecting improved QOL/functioning or decreased symptoms at a given time point will be classified as "improved". Those with no change in score from study entry or a change in score within MID will be classified as "stable". The MID analyses will be conducted in the full population, the population of HR MDS/CMML patients and HR MDS patients.

The change in score from baseline to any post-baseline visit will be presented using cumulative distribution function (CDF) figures. The patient's largest improvement from baseline will be determined first, and CDF curves will then be used to display the cumulative percentage of patients experiencing that improvement by treatment arm. The CDF figures for all subscales will be presented in the full population, the population of HR MDS/CMML patients and HR MDS patients. Additionally, CDF curves will be generated for global health status/QOL score by treatment arm among responders and nonresponders, respectively.

The change from baseline in subscale scores of EORTC QLQ-C30 and QOL-E will be also analysed using the repeated-measures linear mixed-effects (random-intercept only) models by incorporating the measurements across different time points, including treatment arm, time (a discrete variable), the interaction between treatment arm and time, baseline score, and stratification factor as covariates. The estimated mean in the changes from baseline in the 2 treatments and the 95% CIs will be provided at each time point and overall. In addition, the mean differences between treatment groups along with 95% CIs and p values will be presented at each time point and overall in a table and accompanying set of figures. The analyses using repeated-measures linear mixed-effects models will be conducted for all subscales in the full population, the population of HR MDS/CMML and HR MDS patients.

Details of scoring and initial handling of missing data are included in the EORTC QLQ-C30 and QOL-E scoring guidelines. Further investigation of missing patterns and details of imputation, including subsequent sensitivity analysis, may be conducted.

Compliance rates for EORTC QLQ-C30, QQL-E and EQ-5D-5L based on the full ITT population will be summarized over time by treatment arm. Compliance rates will be presented in the full population, the population of HR MDS/CMML patients and HR MDS patients. If compliance is less than 50% at baseline or at either of the first 2 visits, we will not move forward with additional analyses.

7.11.2 Health Economics (Health Care Resource Use)

EQ-5D-5L quality of life questionnaire scores (including 5-dimension descriptive system, VAS score and utilities) will be summarized in descriptive statistics for treatment arms over time. In addition, the change from baseline of VAS score and utilities (time tradeoff) will also be summarized in descriptive statistics for treatment arms over time. Analyses of EQ-5D-5L will be conducted in the full population, the population of HR MDS/CMML patients and HR MDS patients. Specifically, utilities for UK, France, Germany, Italy, and Spain are of interest. The directly elicited value sets will be used for these country-specific utilities calculations, if available, otherwise, the crosswalk value sets will be used.

Healthcare utilization data will be summarized in descriptive statistics of medical encounters. Specifically, the number of hospitalizations, number of ICU stays, number of emergency room stays, length of hospital stay, length of stay in ICU, length of stay in hospital floor bed, visit reasons and primary diagnosis at discharge by treatment arm will be summarized by treatment group over time. The summary of the healthcare utilization data will be conducted in the full population, the population of HR MDS/CMML patients and HR MDS patients.

Transfusion data will be summarized in descriptive statistics. Transfusions will be categorized as platelet (pooled platelet concentrate or plateletpheresis (single donor)) or red blood cell. For each type of transfusion, we will present the number of patients receiving a transfusion, the number of transfusions per patient, the location of the transfusion (in hospital vs. outpatient), and the number of units per transfusion by treatment arm. The summary of the transfusion data will be conducted in the full population, the population of HR MDS/CMML patients and HR MDS patients.

Further modeling will be performed separately at post hoc analyses.

7.11.3 Biomarker

CCI [redacted]

CCI

7.12 Safety Analysis

Safety evaluations will be based on the incidence, severity, type of AEs, clinically significant changes or abnormalities in the patient's physical examination, vital signs, ECG, and clinical laboratory results.

These analyses will be performed using the safety population for all patients, patients with HR MDS/CMML, and patients with HR MDS, separately. All analyses will be performed for by treatment arm.

7.12.1 Adverse Events

7.12.1.1 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 AEs that required dose modification of pevonedistat.
- Treatment emergent AEs that required dose modification of azacytidine.

- SAEs.
- Treatment-emergent drug related SAEs.

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 (HLT), and once within each Preferred Term (PT).

Treatment emergent AEs will be tabulated by SOC, HLT, PT, and highest intensity. Most commonly reported (at least 10% of all patients) treatment emergent AEs will be presented by preferred term. Most commonly reported (at least 10% of all patients) treatment emergent AEs by preferred term will also be summarized by treatment cycles (Cycle 1, Cycle 2-3, Cycle 4-5, Cycle 6-7, Cycle 8-9, Cycle 10-11, Cycle 12-13, Cycle 14+). 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 pevonedistat and on or before the month and year of the date of the last dose of pevonedistat 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 pevonedistat and on or before the year of the date of the last dose of pevonedistat plus 30 days.
- If the start date of an event is completely missing, then the event is assumed to be treatment emergent.

A by-patient listing of the AEs will be presented (the patient listing will contain all AEs, including a flag indicating treatment emergent status).

7.12.1.2 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. Similar summary will be generated for treatment emergent drug related SAEs.

A by-patient listing of the SAEs will be presented (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.

7.12.1.3 Deaths

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status).

All deaths will be summarized by treatment arm, including deaths occurring on-study and death during follow-up separately.

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.

7.12.1.4 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.

7.12.1.5 Haemorrahges (SMQ)

Patients with haemorrhages will be summarized respectively for occurrences of thrombocytopenia, platelet count decreased, and lab platelet toxicity grade of at least 2.

By-patient line listing for patients with Thrombocytopenia/Platelet Count Decreased and Haemorrhages (defined by SMQ Haemorrhages) concurrently occurred within 5 days will be provided.

7.12.1.6 Myalgia and Musculoskeletal Events

A listing of patients who experience treatment emergent myalgia (PT) events or treatment emergent musculoskeletal pain and discomfort (PT) will be presented.

7.12.1.7 Acute Renal Failure Events

A listing of treatment-emergent acute renal failure events will be generated.

7.12.1.8 Liver Function Test (LFT) Elevations

Listing and summary table of treatment-emergent LFT elevations will be generated. The corresponding preferred and HLG terms are listed as below:

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

7.12.1.9 Tachycardia Events

A listing of treatment-emergent tachycardia events will be generated. The corresponding preferred terms are listed as below:

- Heart rate increased.
- Rebound tachycardia.
- Sinus tachycardia.
- Supraventricular tachyarrhythmia.
- Tachyarrhythmia.
- Tachycardia.
- Tachycardia paroxysmal.
- Palpitations.

7.12.1.10 Hypotension

A listing of treatment-emergent hypotension will be generated. The corresponding preferred terms are listed as below:

- Blood pressure ambulatory decreased.
- Blood pressure decreased.
- Blood pressure diastolic decreased.
- Blood pressure orthostatic abnormal.
- Blood pressure orthostatic decreased.
- Blood pressure systolic decreased.
- Hypotension.
- Orthostatic hypotension.

7.12.1.11 Anaemia

A separate table will display a cross-tabulation of patients who report a PT of anemia at the highest intensity and those who receive a concomitant medication of red blood cells at any point during the study.

A listing of treatment-emergent anemia will also be generated. The corresponding preferred terms are listed as below:

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

7.12.1.12 Neutropenia

A listing of treatment-emergent neutropenia will also be generated. The corresponding preferred terms are listed as below:

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

By- patient line listing for patients with Febrile neutropenia and 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 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 Grade 3 or Higher TEAE of Neutropenia (defined by PT Neutropenia, PT Neutrophil Count Decreased, PT White Cell Count Decreased) and 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 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).

7.12.1.13 Change in Transfusion

A listing will be generated for patients who take platelets and/or red blood cells as concomitant medications during study to display transfusion trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+).

7.12.1.14 Overall Summary

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

- Any adverse event (including separate summaries of maximum toxicity grade experienced (Grade 1 to Grade 5)).
- Drug-related adverse event (including separate summaries of maximum toxicity grade experienced (Grade 1 to Grade 5)).
- Serious adverse event.
- Drug related serious adverse event.
- Adverse events resulting in study drug discontinuation.
- Adverse events that required dose modification.
- On-study deaths.

The summary tables will also be provided for overall TEAE summary by age (<65, >=65 and <75, and >=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.

7.12.2 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.

Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratory will be used only when no central laboratory test result exists at the same scheduled sample collection time point.

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:

1. Box graphs of individual tests over time by treatment arm.

2. Scatter plots of baseline versus worst post-baseline values for all patients. Separate plotting characters will be used for each treatment arm. These will be generated for only selected labs (see table below).

Table 7.f 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		
	Direct Bilirubin	X	X		
	Total Bilirubin	X	X		X
	Blood urea nitrogen		X	X	
	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

Additional graphical representations to compare trajectories of platelet count, absolute neutrophil count, and hemoglobin values (eg, median and IQR) over time (eg, by cycle) between treatment arms will be provided.

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:

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

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.

7.12.3 60-day Mortality

Sixty-day mortality rate is defined as the proportion of patients who survive at most 60 days from the first dose of study drug, which will be summarized by treatment arm based on the safety population.

7.12.4 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.

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

7.12.5 12-Lead ECGs

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

QTcF and QTcB will be derived using the following formulas.

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

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

7.12.6 Other Observations Related to Safety

Eastern Cooperative Oncology Group (ECOG) performance status and change from baseline will be summarized. Shifts from baseline to the worst postbaseline score will be tabulated by treatment arm.

7.12.7 Protocol Deviations

A listing will be presented for significant protocol deviation for ITT population, ordered by disease type.

7.13 Interim Analysis

There are two interim analyses (IA) planned for this study.

The first IA is planned for safety, based on 60-day mortality. It is planned when 60 patients are on study for 60 days or do not survive 60 days. This safety evaluation together with the overall data will be reviewed by the independent data monitoring committee (IDMC) that will make recommendations regarding whether the study should continue as planned or discontinue based on the overall data. The IDMC will review the overall profile and if it is deemed unacceptable, the study will stop. Otherwise, enrollment and study procedures will continue as planned during this IA.

The second IA is for evaluation of both efficacy and safety data when approximately 23 EFS events have occurred. The IDMC will review the overall data, and if it is deemed unacceptable, the study will stop. Otherwise, enrollment and study procedures will continue as planned.

7.14 Changes in the Statistical Analysis Plan

Reference materials for this statistical plan include Clinical Study Protocol P-2001 Amendment 4 (Protocol dated 27 July 2018). Additional major changes include:

- Section 7.9.1 prespecify statistical testing procedures to control type I error for US submission and ex-US submission separately.
- Section 7.11.1 by response analysis on patient reported outcomes.
- Section 7.11.1 MID and CDF analyses on the EORTC QLQ C30 subscale scores.

Additional change in SAP Amendment 01, referring the SAP version 1.0 (dated 22 February 2019) include:

- The addition of analyses and summaries for HR MDS patients is to further define results in this subpopulation.
- Section 7.11.1 Patient-Reported Outcomes, clarify the definition of responders for AML patients (CR+PR+CRi).

- Section 7.12.1.9 Tachycardia Events, remove heart rate irregular from the PT search criteria.
- Section 7.12.1.5 Haemorrahges (SMQ) and section7.12.1.12 Neutropenia, clarify that the by-patient line listings are for the concurrent events.

8.0 REFERENCES

1. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65.
2. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108(2):419-25.
3. 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.
4. Liu Y, Hu MX. Testing multiple primary endpoints in clinical trials with sample size adaptation. Pharmaceutical Statistics 2016; 15(1):37-45.
5. Dohner H, Estey E. et al. Diagnosis and management of AML in adults. Blood 2017; 129(4):424-427.
6. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics 1999;55(3):853-7.
7. Robins JM, Hernan M, Brumback B. Marginal strucural models and causal inference in epidemiology. Epidemiology 2000; 11(5): 550-560.
8. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics 2000;56(3):779-88.
9. 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.
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. 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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	24-Sep-2019 15:23 UTC