Title: A Phase 1/1b, Open-label Study of Pevonedistat (MLN4924, TAK-924) as Single Agent and in Combination with Azacitidine in Adult East Asian Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS)

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

STATISTICAL ANALYSIS PLAN

A Phase 1/1b, Open-label Study of Pevonedistat (MLN4924, TAK-924) as Single Agent and in Combination with Azacitidine in Adult East Asian Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS)

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE(s)	Adverse event (or events)
ALT	Alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the plasma concentration-time curve
AUMC	Area under the first moment curve
BNP	B-type natriuretic peptide
BSA	body surface area
C_{max}	Maximum plasma concentration
CL	Total clearance (after IV administration)
CMML	chronic myelomonocytic leukemia
CPK	Creatine phosphokinase
Cr	Creatinine
CR	complete remission
CRi	complete remission with incomplete recovery
CRF	Case Report Form
CRM	Continual Reassessment Method
CRP	C-reactive protein
CV	coefficient of variation
DBP	diastolic blood pressure
DIC	disseminated intravascular coagulation
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELN	European Leukemia Net
EOS	End of study
FAB	French-American-British
HLT	high level term
IDMC	Independent Data Monitor Committee
IPSS-R	International Prognostic Scoring System
IV	intravenous
IWG	International Working Group
LLQ	limit of quantification
LPO	last patient out
LVEF	left ventricular ejection fraction
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
miR	microRNA
MDS	Myelodysplastic Syndromes

Abbreviation	Term
MRT	mean residence time

MTD	Maximum Tolerated Dose
NAE	Nedd8-Activating Enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	Progressive Disease
PK	Pharmacokinetic
PR	Partial Remission
PT	preferred term
PT	prothrombin time
ORR	Overall Response Rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
SAE	serious adverse event
SBP	systolic blood pressure
SC	Subcutaneously
SD	stable disease
SOC	system organ class
$t_{1/2z}$	Terminal elimination half-life
t_{max}	Time to reach C_{max}
TAD	time after dosing
Vss	volume of distribution at steady state (after IV administration)
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

In general, the purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This is a multicenter, open-label, phase 1/1b dose escalation and expansion study of pevonedistat administered IV as a single agent and in combination with azacitidine in adult East Asian patients with World Health Organization (WHO)-defined AML or High Risk (HR) MDS (Revised International Prognostic Scoring System [IPSS-R] very high/high/intermediate)

It is expected that approximately 37 patients will be enrolled in this study. Once enrolled, patients will be administered pevonedistat (administered via 60-minute IV infusion) with or without azacitidine (administered IV or SC).

The Single-Agent Arm will include East Asian patients with R/R AML or R/R HR MDS (including nonproliferative chronic myelomonocytic leukemia [CMML]). In the Single-Agent Arm, each 21-day treatment cycle includes treatment with pevonedistat (starting dose of 25 mg/m^2) on Days 1, 3, and 5, followed by a rest period of 16 days. Samples for PK will be collected at prespecified time points during Cycle 1. Enrollment in the second dose level (44 mg/m^2) will only begin after the data from the first group of 3 patients in the Single-Agent Arm has been reviewed and the dose has been found to be safe and tolerable.

In parallel with the opening of enrollment for the second dose level in the Single-Agent Arm, enrollment will begin for the first dose level of the Combination Arm. The Combination Arm will include East Asian patients with R/R AML or R/R HR MDS (including R/R nonproliferative CMML) as well as previously untreated AML or HR MDS (including nonproliferative CMML). In the pevonedistat+azacitidine Combination Arm, each 28-day treatment cycle includes the following: treatment with pevonedistat (starting

dose of 10 mg/m^2) on Days 1, 3, and 5; treatment with azacitidine (75 mg/m^2 [IV during Cycle 1; IV or SC in Cycles 2 and beyond, per the investigator's choice]) on Days 1 through 5, and 8 through 9; and a rest period of 19 days. Samples for PK will be collected at prespecified time points during Cycle 1. Enrollment in the Combination Arm will not begin until 3 patients have successfully completed Cycle 1 of the 25 mg/m^2 Single-Agent Arm.

The 3+3 approach will be used during the dose escalation phase. The dose level(s) determined to be safe during the dose escalation phase of the study may then be expanded to as many as 12 patients in total to further confirm safety and investigate PK. Based on the geographic distribution of patients in the dose escalation/expansion phases (Single-agent and/or Combination Arms) and emerging PK and safety data, additional patients may be added in the expansion phase, as needed, to further characterize the PK, safety, and tolerability in a particular East Asian geographic region.

In the Single-Agent Arm, at least 1 Japanese patient will be included in each group of 3 patients in the dose escalation phase. If a dose expansion group of up to 6 patients is added at the highest dose level, at least 1 additional Japanese patient will be included, unless at least 3 Japanese patients were enrolled at that dose level during dose escalation and emerging data support an adequate characterization of PK and safety; in this case, no additional Japanese patients are needed in the expansion phase.

In the Combination Arm, at least 1 Japanese patient will be included in each group of 3 patients in the dose escalation phase. Following dose escalation, an additional group of up to 6 patients will be added in the expansion phase, for a total of up to 12 patients at the highest dose level. The total number of Japanese patients at the highest dose level will be at least 6.

No formal interim analysis is planned, but safety and PK data will be reviewed on an ongoing basis during the dose escalation and expansion phases of the study.

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.

Adverse events will be assessed, and laboratory values, vital signs, and ECGs will be obtained, to evaluate the safety and tolerability of pevonedistat administered as a single agent or in combination with azacitidine.

Disease response assessments will be conducted using International Working Group (IWG) criteria for AML and modified IWG criteria for MDS (including CMML). Patients, including those who achieve a Complete Remission (CR), may receive pevonedistat and/or azacitidine until they experience disease progression or symptomatic deterioration. Study drug may be discontinued if a patient experiences study drug-related toxicity or if, in the opinion of the investigator or sponsor, continuation on study may jeopardize the safety of the patient. Patients may discontinue therapy at any time for any reason. Patients will attend the End of Study (EOS) visit for safety 30 days (+10 days) after receiving their last dose of study drug.

1.2 Study Objectives

1.2.1 Primary Objectives

- To evaluate safety and tolerability of pevonedistat administered as a single agent in East Asian patients with R/R AML or R/R HR MDS.
- To evaluate safety and tolerability and determine the recommended phase 2/phase 3 dose of pevonedistat administered in combination with azacitidine in East Asian patients with AML or HR MDS.
- To characterize the PK of pevonedistat administered as a single agent or in combination with azacitidine in East Asian patients.

1.2.2 Secondary Objectives

The secondary objective is to evaluate disease response in both AML and MDS that may be observed with the single-agent pevonedistat or with a combination of pevonedistat and azacitidine.

[redacted]

2. POPULATIONS FOR ANALYSIS

2.1 Intent-to-Treat Population

Not applicable for a phase 1/1b study.

2.2 Per-Protocol Population

Not applicable for a phase 1/1b study.

2.3 Response-Evaluable Population

The response-evaluable population is defined as all patients who receive at least 1 dose of study drug, have a baseline disease assessment, and have at least 1 post-Baseline disease assessment.

Response analyses will be performed using the response-evaluable population.

2.4 Safety Population

The safety population is defined as all enrolled patients who receive at least 1 dose of study drug.

All safety and efficacy analyses will be performed using the safety population.

2.5 Pharmacokinetic-Evaluable Population

The PK-evaluable population is defined as all enrolled patients who have sufficient dosing in Cycle 1 and pevonedistat concentration-time data to reliably estimate PK parameters by noncompartmental analysis methods and who have not received any excluded concomitant medications per the protocol

PK analyses will be performed using the PK-evaluable population.

2.6 Pharmacodynamics Population

Not applicable for this study.

2.7 DLT Evaluable Population

The DLT-evaluable population is defined as patients who either experience DLT during Cycle 1 or receive all scheduled doses of study drug in Cycle 1 without DLT.

3. HYPOTHESES AND DECISION RULES

Not applicable for a phase I study.

4. INTERIM ANALYSIS

As this is a phase I study there is no formal interim analysis. There will be an ongoing review of safety data with the medical monitor and study investigators, as well as within an internal Safety Working Group and the Independent Data Monitor Committee (IDMC).

5. STATISTICAL METHODOLOGY

Analyses will be primarily descriptive in nature. No formal statistical tests will be performed. 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 percent (calculated using non-missing values) per category for categorical data, unless specified otherwise.

Due to the use of the 3+3 methodology for dose escalation, at a minimum, three patients will be dosed at any given dose level. Data may be pooled across dose levels and treatments for summary purposes. When appropriate, data will be summarized for the pooled dose levels below the highest tolerable dose, at highest tolerable dose, and for all patients. Data from each schedule may be summarized separately. Patients will be analyzed at the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

5.1 Sample Size Justification

It is anticipated that approximately 37 patients will be enrolled to the dose-escalation and expansion cohorts for the determination of the highest tolerable dose of single-agent arm and combination arm and further evaluation of this dose.

This study uses a 3+3 design to identify the tolerated dose in the dose escalation phase for single-agent pevonedistat and the pevonedistat+azacitidine combination. The tolerated dose is defined as the highest dose that generates a DLT rate of ≤25% during Cycle 1. The

escalation starts with single-agent pevonedistat (group of 3 patients) at 25 mg/m^2. If this dose is safe and tolerable, the escalation will then be split into 2 independent arms: single-agent pevonedistat and pevonedistat+azacitidine combination. At the highest tolerated dose level, an additional 3 patients will be added during the dose escalation phase to confirm safety and tolerability. Assuming this study schema and also assuming an additional 6 patients in the dose expansion phase, the estimated number of patients for the study via simulation is 30 to 33. To further allow for other considerations, such as the number of PK-evaluable patients and number of patients required per country or East Asian race group at the highest dose level, the estimated number of patients to be enrolled in this study is approximately 37.

5.2 Randomization and Stratification

No randomization or stratification will be performed in this study.

5.3 Unblinding

As this is an open-label study, no unblinding methodology is required.

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing efficacy and safety data will be performed unless specified otherwise. The relevance of missing sample data will be assessed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

5.4.2 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 average of the screening and Cycle 1 Day 1 predose value.

5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected. The analysis of PK data and determination of PK parameters will be based on the actual elapsed time post dose.

5.4.4 Justification of Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

5.4.5 Withdrawals, Dropouts, Loss to Follow-up

Patients in the escalation phase who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced. Generally, no additional patients will be enrolled due to withdrawals, dropouts, or loss to follow-up.

5.5 Patient Disposition

A tabulation of patient disposition data will include the number of patients for the following categories: patients treated (safety population), patients in the DLT-evaluable population, patients in the PK-evaluable population, patients in the response-evaluable population, and patients discontinued from the study. The primary reason for study discontinuation will also be summarized in this table.

All data will be summarized by each dose level and treatment, and also by Japanese and non-Japanese patients. Percentages will be based on the number of patients in the safety population, and they will be calculated for highest tolerable dose, and the study total.

Data concerning patient disposition (e.g. reason for study termination, patient population) will be presented in by-patient listings.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Baseline demographics will be summarized by each dose level and treatment, and also by Japanese and non-Japanese ethnicities for all patients in the safety population. Baseline demographic data to be evaluated will include age at date of informed consent, sex, ethnicity, race, height, weight, baseline disease characteristics and body surface area (BSA).

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 Cycle 1 Day 1 pre-dose 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.

5.6.2 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, along with whether an exception was obtained.

5.6.3 Medical History

5.6.3.1 General Medical History

Patients with a medical (and/or surgical) history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the outcome status (whether it is resolved or ongoing).

5.6.3.2 Disease-Specific History

Not applicable for this study.

5.6.4 Baseline Disease Status

Baseline disease characteristics (MDS: disease type such as de novo MDS or secondary MDS, disease subtype will be summarized for secondary MDS, months from initial diagnosis, French-American-British (FAB) category, WHO classification, revised WHO classification and IPSS-R category; AML: disease type such as de novo AML or secondary AML, disease subtype will be summarized for secondary AML, months from initial diagnosis, revised WHO classification and evidence of extramedullary disease) will be

summarized for all patients in the safety population. ECOG performance status will be summarized similarly in the same table. Both Baseline disease characteristics and ECOG status will also be summarized by Japanese and non-Japanese patients. Separate by-patient listings will also be presented for baseline disease characteristics and ECOG performance status.

Separate tables for MDS and AML will summarize the numbers and percentages of patients who had prior therapy (including months from last dose of chemotherapy to first dose of pevonedistat), 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. These tables will also be summarized by Japanese and non-Japanese patients. Separate by-patient listings will also be presented for prior therapies, prior radiation, prior surgery, and prior transplants.

[redacted]

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

[redacted]

AML patients will be classified into 3 categories: Adverse, Intermediate and Favorable based on the 2017 European LeukemiaNet (ELN) risk stratification by genetics algorithm.

The ELN risk classification results will be summarized by dose group and treatment and all patients, and also by Japanese and non-Japanese patients, and will also be included in a by-patient listing. The ELN risk classification criteria use the version published by Döhner, et al., 2017.

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

5.7 Treatments and Medications

5.7.1 Concomitant Medications

All concomitant medications will be mapped to preferred terms according to the World Health Organization (WHO) drug dictionary. The number and percentage of patients in the safety population taking concomitant medications will be tabulated by WHO drug generic term. Tabulations will be performed for all patients in the safety population by dose and treatment. Hydroxyurea use will also be captured in this table. Concomitant procedures will not be coded.

Concomitant medications and procedures will be presented in separate by-patient listings.

5.7.2 Study Treatments

Patients will be administered pevonedistat (administered via 60-minute IV infusion) with or without azacitidine (administered IV or SC).

In the Single-Agent Arm, each 21-day treatment cycle includes treatment with pevonedistat on Days 1, 3, and 5, followed by a rest period of 16 days.

In the pevonedistat+azacitidine Combination Arm, each 28-day treatment cycle includes the following: treatment with pevonedistat (starting dose of 10 mg/m^2) on Days 1, 3, and 5; treatment with azacitidine (75 mg/m^2) on Days 1 through 5, and 8 through 9; and a rest period of 19 days.

All dosing information for each visit will be presented in a by-patient listing.

5.7.2.1 Duration of Follow-up

The duration of follow-up is defined as time from the date of first dose of study treatment 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 first dose + 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 first dose + 1, with a censor variable = 0 (event for follow-up).

5.7.2.2 Extent of Exposure

The extent of exposure to pevonedistat will be based on the number of cycles and the mean number of doses administered per cycle. The distribution of the number of cycles received will be presented by dose level or treatment to which patients were initially assigned, as well as for all patients. Patients will be considered to have been treated for a cycle if they receive at least one dose of pevonedistat during that cycle. Percentages will be calculated by dose level and treatment and for all the patients.

The mean number of doses per cycle will be calculated for each patient and summarized for each dose levels and treatments and the study total.

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 at baseline, 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:

$$\text{Total Dose Received} = \text{Sum of Daily Dose Received across all days that pevonedist at was administer ed}$$
$$\text{Total Dose Expected} = \text{Daily Expected Dose} * 3 \text{ doses per cycle} * \text{number of treated cycles}$$
$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

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 by dose level and treatment, as well as for all patients.

For azacitidine dosing, the percentage of all doses that were administered IV or SC will be calculated for the combination arms. The extent of exposure will be summarized separately for IV and SC in a similar manner as pevonedistat. A separate column will be generated for each dose level of pevonedistat, and the number of cycles of azacitidine administered will be summarized.

The mean number of doses per cycle will be calculated for each patient and summarized by pevonedistat dose level and the study total.

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

$$\text{Daily Expected Dose} = 75 \text{ mg/m}^2 * \text{BSA}$$
$$\text{Total Dose Received} = \text{Sum of Actual Dose across all days of dosing}$$
$$\text{Total Dose Expected} = \text{Sum of "Daily Expected Dose} * 7 \text{ doses per cycle" across all treated cycles}$$
$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

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

5.7.2.3 Treatment Compliance and Modifications

The actions on study drugs (Dose Held, Dose Missed, Dose Reduced, Dose Interrupted, Dose Delayed, Dose Incomplete, or Discontinued) will be summarized by dose level for pevonedistat, azacitidine IV, and azacitidine SC respectively. Data will be summarized for

Cycle 1 only as well as all cycles combined. A patient will count only once for each type of action.

5.8 Efficacy Analyses

Since this is a phase I study, efficacy is not a primary endpoint. A summary of the best overall response as determined by the investigator using the Revised IWG guidelines will be presented as a measure of antitumor activity of pevonedistat.

For AML patients, response will be based on the best overall response as determined by the investigator using the Revised Recommendations of IWG response criteria for AML. The number and percentage of patients in each disease response category (e.g. complete remission [CR], CR with incomplete recovery [CRi], partial remission [PR], stable disease [SD], clinical benefit despite PD, progressive disease [PD] and relapse after CR) and ORR (CR+PR) will be presented for each dose level and treatment and all patients, and also summarized by Japanese and non-Japanese patients.

For MDS patients, response will be based on the best overall response as determined by the investigator using the revised IWG response criteria for MDS. The number and percentage of patients in each disease response category (e.g. complete remission [CR], partial remission [PR], marrow CR, stable disease [SD], relapse after CP/PR, [redacted] and progressive disease [PD]) and ORR (CR+ PR+Hematologic Improvement [HI]) will be presented for each dose level and treatment and all patients, and also summarized by Japanese and non-Japanese patients.

For the disease response CR and ORR, AML patients and MDS patients will be combined and the number of patients and percentage will be presented for each dose level and treatment and all patients, and also summarized by Japanese and non-Japanese patients.

For each AML patient in the response-evaluable population, the best percent change (i.e., largest reduction) from baseline in the myeloblast count from bone marrow aspirates will be calculated and displayed in separate waterfall plots to show the distribution of response across all patients. The waterfall plots will be generated by dose level of pevonedistat and the study total, and also by Japanese and non-Japanese patients. A separate set of plots will be generated for MDS patients. Unscheduled visits will also be included in such displays. Bone marrow aspirate myeloblast counts and percent change from baseline in myeloblast count will be summarized over time separately for AML and MDS patients, and by Japanese

and non-Japanese patients. A separate set of waterfall plots for the combined AML and MDS patients will also be generated.

If bone marrow aspirate myeloblast counts is <1%, a conservative value of 1% will be assigned. If bone marrow aspirate myeloblast count is UNABLE TO DETECT, 0% will be assigned.

Differential counts taken from bone marrow aspirate samples will be displayed in lines over time for patients by dose level of pevonedistat. The average line and the median line will also be drawn in different colors from the lines for individual patients. Cell types examined will include myeloblasts, promyelocytes, myelocytes, metamyelocytes, neutrophil bands, and segmented neutrophils. For myeloblasts (bone marrow aspirate samples), separate line graphs will be generated for each patient by dose level. Bone marrow differential counts will also be presented in by-patient listings.

The duration of response will be summarized for each dose and treatment for all patients, and by Japanese and non-Japanese patients, and will also be presented in a by-patient listing for all response-evaluable patients with disease response (CR or PR in AML and MDS patients). For AML and MDS patients, duration of response is the time (in both days and months) from the date of first documented response per the investigator response assessment to the date of first documentation of progressive disease (PD, including clinical benefit despite PD responses) after the first documented response or, if the patient discontinues treatment, the date of last disease assessment. The duration of response (in months), time to first response (in months) and the number of cycles of response will also be included. In addition, the date of first response, the date of progressive disease, and the number of cycles of response will be shown in the by-patient listing.

The duration of SD or better will be presented in a by-patient listing for all response-evaluable patients. Duration of SD or better is the time from the date of first dose to the date of first documentation of PD (including clinical benefit despite PD responses), or the date of last disease assessment if the patient discontinues treatment before PD. In addition, the date of first dose, the date of first SD or better, the date of first documentation of PD, and the number of cycles with SD or better will be shown. The duration of SD or better (in months) and the number of cycles with SD or better will also be summarized descriptively for each dose level and treatment and by Japanese and non-Japanese for all response-evaluable patients.

[redacted]

Pre-treatment disease status assessment and disease response category will be presented in by-patient listings.

5.8.1 Primary Efficacy Endpoint

Not applicable for this study.

5.8.2 Secondary Efficacy Endpoints

- ORR (CR+PR [for AML] or CR+PR+hematologic improvement [HI] [for MDS]).
- CR.

5.8.3 Other Efficacy Endpoints

Not applicable for this study.

5.9 Pharmacokinetic [redacted]

5.9.1 Pharmacokinetic Analyses

Serial blood samples (~ 3 mL) for the determination of plasma concentrations of pevonedistat will be collected only during Cycle 1 of the study for Schedules A (single – agent pevonedistat arm) and B (pevonedistat + azacitidine combination arms)

Single-Agent Pevonedistat Arm, Cycle 1

- Day 1:
  - Within 1 hour before the start of pevonedistat infusion
  - At the end of the pevonedistat infusion (immediately before stopping the IV infusion)
  - At 1 hour (± 10 minutes), 2 hours (± 20 minutes), 4 hours (± 30 minutes), 6 hours (± 30 minutes), and 10 hours (± 30 minutes) after completion of the pevonedistat infusion
- Day 2:
  - 24 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 1 infusion.

- Day 3:
    - 48 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 1 infusion. The sample is to be collected Within 10 minutes before the start of the pevonedistat infusion
- Day 5:
    - Within 10 minutes before the start of pevonedistat infusion
    - At the end of the pevonedistat infusion (immediately before stopping the IV infusion)
    - At 1 hour (± 10 minutes), 2 hours (± 20 minutes), 4 hours (± 30 minutes), 6 hours (± 30 minutes), and 10 hours (± 30 minutes) after completion of the pevonedistat infusion
- Day 6: 24 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 5 infusion
- Day 7: 48 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 5 infusion

Pevonedistat +Azacitidine Combination Arm, Cycle 1

- Day 1:
    - Within 1 hour before the start of pevonedistat infusion and before azacitidine administration
    - At the end of the pevonedistat infusion (immediately before stopping the IV infusion)
    - At 1 hour (± 10 minutes), 2 hours (± 20 minutes), 4 hours (± 30 minutes), 6 hours (± 30 minutes), and 10 hours (± 30 minutes) after completion of the pevonedistat infusion
- Day 2:
    - 24 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 1 infusion. The sample is to be collected within 10 minutes before the start of azacitidine administration
- Day 3:
    - 48 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 1 infusion. The sample is to be collected within 10 minutes before the start of azacitidine administration
- Day 5:
    - The sample is to be collected within 10 minutes before the start of azacitidine administration
    - At the end of the pevonedistat infusion (immediately before stopping the IV infusion)

  - At 1 hour (± 10 minutes), 2 hours (± 20 minutes), 4 hours (± 30 minutes), 6 hours (± 30 minutes), and 10 hours (± 30 minutes) after completion of the pevonedistat infusion

- Day 6: 24 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 5 infusion
- Day 7: 48 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 5 infusion

The PK-evaluable population will be used for the PK analysis (see Section 2.5).

Individual concentration-time data of pevonedistat administered alone or in combination with azacitidine will be analyzed by noncompartmental methods [redacted]

Plasma concentration values below the lower limit of quantification (<LLQ) of the bioanalytical assay will be set to zero for analysis. Actual PK sampling times will be used in the derivation of PK parameters. The exact date and time of each sample collection, as well as the actual start and stop times of the infusion, should be recorded accurately, and particular care should be given to the recording of blood sampling times that occur close to the infusion. Actual time after dosing (TAD) will be set to zero for pre-infusion samples and calculated as the difference between the sample collection date/time and the start date/time of the IV infusion.

The following plasma PK parameters will be estimated, as permitted by the data:

Parameters	Definition	Method of Determination
C_{max}	Maximum observed concentration (theoretically end-of-infusion concentration)	Observed directly from data
T_{max}	Time at which C_{max} occurs (theoretically infusion time)	Derived from the stop time of the IV infusion
AUC_{last}	Area under the plasma concentration-time curve from time zero to the last measurable concentration	Linear-log trapezoidal method
AUC_{τ}	Area under the plasma concentration-time curve from time zero to the end of the dosing interval (τ), where τ is equal to 48 hours	Linear-log trapezoidal method
AUC_{24}	Area under the plasma concentration-time curve from time zero to 24 hours post-dose	Linear-log trapezoidal method
AUC_{∞}	Area under the plasma concentration-time curve extrapolated to infinity	$AUC_{last} + C_{last}/lambda_z$, where AUC_{last} is the AUC from time zero the last measurable concentration (C_{last})
$Lambda_z$	Terminal disposition phase rate constant	Estimated as the slope of a linear regression of the log-linear concentration-time profile
$t_{1/2z}$	Terminal disposition phase half-life	$ln(2) / lambda_z$

Parameters	Definition	Method of Determination
$R_{ac\ (AUC)}$	Observed accumulation ratio (based on AUC)	AUC_{τ} (Day 5) / AUC_{τ} (Day 1)
CL	Total clearance (after IV administration)	Dose / AUC_{∞} after single dosing or dose / AUC_{last} after multiple dosing
Vss	Volume of distribution at steady-state (after IV administration)	CL*MRT where the mean residence time (MRT) is derived as $AUMC_{\infty}$ / AUC_{∞} - TI/2 with TI the infusion duration and $AUMC_{\infty}$ the area under the first moment curve from time zero to infinity calculated by trapezoidal method.

To report lambdaz, $t_{1/2z}$, AUC_{∞}, CL, and V_{ss}, the terminal disposition phase data time span must be greater than or equal to 2, the number of data points included in the calculation must be at least 3, and R^2 must be greater than or equal to 0.8.

Individual pevonedistat plasma concentration-time data (including nominal and actual times; TAD derived as shown in table below) and individual plasma PK parameters will be listed by patient ID and summarized descriptively by treatment arm (Single-agent and Combination arms), dose level and study day (Cycle1, Day 1 or Day 5 up to 48 hours) for overall, Japanese and other Asian population respectively as deemed appropriate (or as data permit.

Nominal TAD*	**Treatment arm**	**Day**	**Protocol Specified Time Point**
0 hour	A (single agent arm)	1	Within 1 hour before the start of pevonedistat infusion
	B (combination arm)	1	Within 1 hour before the start of pevonedistat infusion and before azacitidine administration
0 hour	A	5	Within 10 minutes before the start of pevonedistat infusion
	B	5	Within 10 minutes before the start of azacitidine administration
1 hour	A, B	1, 5	At the end of the pevonedistat infusion (immediately before stopping the IV infusion)
2 hours	A, B	1, 5	1 hour after completion of the pevonedistat infusion
3 hours	A, B	1, 5	2 hours after completion of the pevonedistat infusion

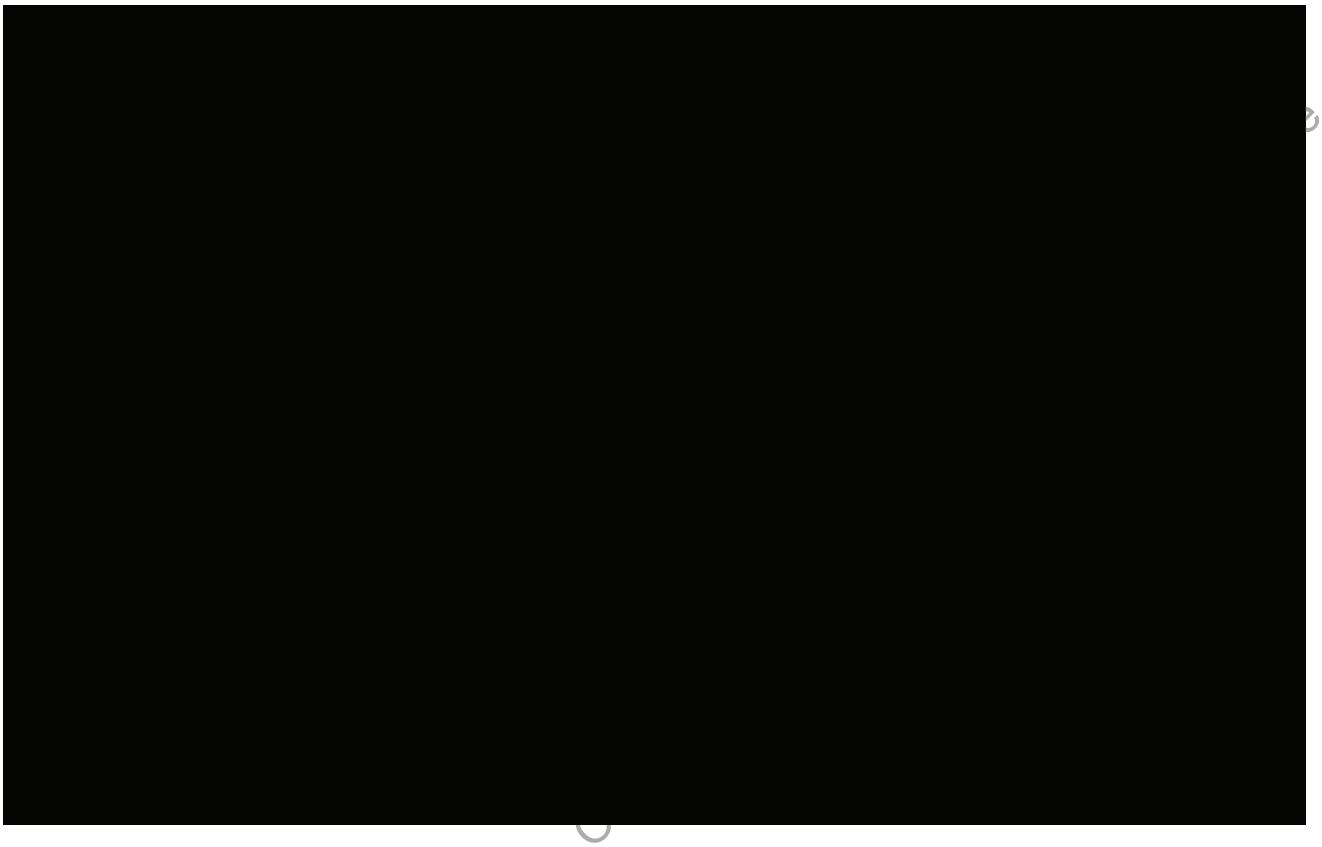
Nominal TAD*	Treatment arm	Day	Protocol Specified Time Point
5 hours	A, B	1, 5	4 hours after completion of the pevonedistat infusion
7 hours	A, B	1, 5	6 hours after completion of the pevonedistat infusion
11 hours	A, B	1, 5	10 hours after completion of the pevonedistat infusion
24 hours	A	2	24 hours after initiation of pevonedistat Cycle 1, Day 1 infusion
		6	24 hours after initiation of pevonedistat Cycle 1, Day 5 infusion
24 hours	B	2	24 hours after initiation of pevonedistat Cycle 1, Day 1 infusion. Within 10 minutes before the start of azacitidine administration
		6	24 hours (± 1 hour) after initiation of pevonedistat Cycle 1, Day 5 infusion
48 hours	A	3	48 hours after initiation of pevonedistat Cycle 1, Day 1 infusion. Within 10 minutes before the start of the pevonedistat infusion
		7	48 hours after initiation of pevonedistat Cycle 1, Day 5 infusion
48 hours	B	3	48 hours after initiation of pevonedistat Cycle 1, Day 1 infusion. Within 10 minutes before the start of azacitidine administration
		7	48 hours after initiation of pevonedistat Cycle 1, Day 5 infusion

*For concentration measurements concurrent with bone marrow aspirates, nominal TAD will not be assigned and will be summarized separately.

Summary statistics (N, arithmetic mean, standard deviation, geometric mean [where appropriate], coefficient of variation [CV], median, minimum, and maximum) will be calculated if there is less than 50% of the values missing as described previously. The arithmetic mean and geometric mean will be reported on at least 2 non-missing values; and the median, standard deviation and CV will be reported on at least 3 non-missing values. The summary statistics will be calculated for overall, Japanese and other Asian population respectively as deemed appropriate (or as data permit).

For each of the treatment arms, individual and mean pevonedistat plasma concentration-time data will be plotted over time (using nominal time for mean and actual TAD for individual data) by treatment arm, dose level and study day using linear and semi-logarithmic scales for overall, Japanese and other Asian population respectively as deemed appropriate (or as data permit). Box plots of pevonedistat dose-normalized AUC and C_{max} on Day 1 and Day 5, Cycle 1 will be provided for overall, Japanese and other Asian population respectively as permitted by data.

[redacted]



5.10 Safety Analyses

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and changes from Baseline in the patient's vital signs, weight, and clinical laboratory results using the Safety population.

5.10.1 Adverse Events

5.10.1.1 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 up through 30 days (+10 days) after the last dose of study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline.

AEs will be tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT) for all patients and also by Japanese and non-Japanese patients. Summary tabulations include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- Grade 4 or higher treatment-emergent AEs
- Grade 4 or higher drug-related treatment-emergent AEs
- Grade 3 drug-related treatment-emergent AEs
- Grade 4 drug-related treatment-emergent AEs
- Grade 5 drug-related treatment-emergent AEs
- Treatment-emergent AEs resulting in study drug discontinuation
- SAEs
- Drug-related SAEs
- The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥ 10% of all patients).

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated by SOC, HLT, PT. The most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term. The 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+). 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.

5.10.1.2 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 for all patients and also by Japanese and non-Japanese patients. 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.

5.10.1.3 Deaths

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

5.10.1.4 Treatment-Emergent Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of patients experiencing at least one treatment-emergent adverse event resulting in discontinuation of study drug will be summarized by MedDRA SOC, HLT, and PT for all patients and also by Japanese and non-Japanese patients.

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented. All treatment-emergent AEs resulting in discontinuation of study drug occurring on-study and during follow-up will be displayed.

5.10.1.5 Dose Limiting Toxicities (DLTs)

DLT in Cycle 1 will be tabulated for each dose group and treatment (single agent or combination). The number and percentage of DLT will be summarized by preferred term of individual toxicities for each dose group and treatment for all patients and also by Japanese and non-Japanese patients.

A by-patient listing of DLTs in Cycle 1 will be presented by dose group and treatment for all patients and also by Japanese and non-Japanese in the DLT-evaluable population. Patients will be grouped by the dose group and treatment to which they were originally assigned at enrollment.

The DLT-Evaluable population will be used for the analysis of DLTs.

5.10.1.6 Hemorrhages

Patients of with hemorrhagic events (SMQ Hemorrhages) will be summarized respectively for occurrences of thrombocytopenia, platelet count decreased, and lab platelet toxicity grade of at least 2.

5.10.1.7 Myalgia and Musculoskeletal Pain Events

A listing of patients who experience treatment emergent myalgia, arthralgia, and musculoskeletal pain events will be presented.

5.10.1.8 **Acute Renal Failure Events**

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

- Acute kidney injury
- Acute phosphate nephropathy
- Acute prerenal failure
- Anuria
- Azotemia
- Continuous hemodiafiltration
- Dialysis
- Hemodialysis
- Neonatal anuria
- Nephropathy toxic
- Oliguria
- Peritoneal dialysis
- Prerenal failure
- Renal failure
- Renal failure acute
- Renal failure neonatal
- Renal impairment
- Renal impairment neonatal
- Albuminuria
- Blood creatinine abnormal
- Blood creatinine increased
- Blood urea abnormal
- Blood urea increased
- Blood urea nitrogen/creatinine ratio increased
- Creatinine renal clearance abnormal
- Creatinine renal clearance decreased
- Creatinine urine abnormal
- Creatinine urine decreased
- Crystal nephropathy
- Glomerular filtration rate abnormal
- Glomerular filtration rate decreased
- Hypercreatininaemia
- Nephritis
- Oedema due to renal disease
- Protein urine present
- Proteinuria
- Renal function test abnormal
- Renal transplant
- Renal tubular disorder
- Renal tubular necrosis
- Tubulointerstitial nephritis
- Urea renal clearance decreased
- Urine output decreased

5.10.1.9 Liver Function Test (LFT) Elevations

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

- Acute hepatic failure
- Hyperbilirubinemia
- Liver function test
- Liver function test abnormal
- Alanine aminotransferase
- Alanine aminotransferase abnormal
- Alanine aminotransferase increased
- Aspartate aminotransferase
- Aspartate aminotransferase increased
- Mitochondrial aspartate aminotransferase increased
- Aspartate aminotransferase abnormal
- Blood alkaline phosphatase
- Blood alkaline phosphatase abnormal
- Blood alkaline phosphatase increased
- Blood bilirubin
- Bilirubin urine
- Bilirubin conjugated
- Blood bilirubin abnormal
- Blood bilirubin increased
- Urine bilirubin increased
- Bilirubin conjugated increased
- Blood bilirubin unconjugated increased
- Gamma-glutamyl transferase
- Gamma-glutamyl transferase abnormal
- Gamma-glutamyl transferase increased
- Hepatic enzyme increased
- Hepatic function abnormal

5.10.1.10 Tachycardia Events

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

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

5.10.1.11 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 orthostatic decreased
- Blood pressure systolic decreased

- Blood pressure diastolic decreased
- Blood pressure orthostatic abnormal
- Hypotension
- Orthostatic hypotension

5.10.1.12 **Anemia**

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:

- Anemia of chronic disease
- Anemia of malignant disease
- Anemia
- Red blood cell count decreased
- Hemoglobin decreased
- Mean cell hemoglobin decreased
- Hematocrit decreased

5.10.1.13 **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
- Febrile neutropenia
- Neutropenia
- Neutropenic infection
- Neutropenic sepsis
- Neutrophil count abnormal
- Neutrophil count decreased
- Neutrophil percentage abnormal
- Neutrophil percentage decreased

5.10.1.14 Overall Summary

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

- 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
- Treatment-emergent adverse events resulting in study drug discontinuation
- On-study deaths

Percentages will be calculated for all the patients and all the highest tolerable dose patients.

5.10.2 Laboratory Data

For the purposes of summarization, 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 summarization, ignoring the non-numeric qualifier.

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

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from Baseline to the worst post-Baseline value. 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 mean laboratory values over time for key laboratory parameters by dose group and treatment.

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

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	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
	Hematocrit		X		
	Hemoglobin	X	X		
	Leukocytes	X	X		
	Lymphocyte Count	X	X		
	Neutrophils (ANC)	X	X		x
	Monocytes		X		
	Eosinophils		X		
	Basophils		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)

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

Cockcroft-Gault equation:

For males:

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

OR

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

For females:

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

OR

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

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:

$$\text{GFR (mL/min/1. 73 m}^2) = 141 \text{ x min(Scr/0. 9, 1)}^{-0.411} \text{ x max(Scr/0. 9, 1)}^{-1.209} \text{ x } 0.993^{\text{Age}} \text{ ,}$$

where Scr = serum creatinine (mg/dL).

For black males:

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

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.

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

A separate listing of selected urinalysis parameters will be generated, including protein, occult blood, and leukocytes.

A by-patients listing of urine microscopic analysis parameters will be generated, which include the patient ID, visit, and erythrocytes, leukocytes, bacteria, casts, and crystals.

5.10.3 Electrocardiograms

The number and percent of patients experiencing abnormal ECG results will be summarized for each scheduled time point by dose group and treatment.

QTcF and QTcB will be derived using the following formulas.

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

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

5.10.4 Vital Signs

Boxplots over time for temperature, DBP, SBP, and heart rate during Cycle 1 will be generated at the highest tolerable dose for each arm (single-agent arm and combination arm). These will be summarized for measurements taken in the sitting position.

In addition, orthostatic hypotension will be defined as a decrease in systolic blood pressure of at least 20 mm Hg or in diastolic blood pressure of at least 10 mm Hg after the patient changes from a supine position to a standing position. Orthostatic heart rate will be defined as increase in heart rate of at least 20 beats/min after the patient changes from a supine position to a standing position.

A table will be generated to summarize the following at baseline and post dose for each dose group and treatment:

- Percentage of patients who experienced orthostatic hypotension at baseline
- Percentage of patients who had orthostatic heart rate at baseline
- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate at baseline
- Percentage of patients who experienced orthostatic hypotension post dose
- Percentage of patients who had orthostatic heart rate post dose
- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate post dose

Moreover, the summary table should also include the following:

- Percentage of patients who had orthostatic hypotension post dose and did not have orthostatic hypotension at baseline
- Percentage of patients who had orthostatic heart rate post dose and did not have orthostatic heart rate at baseline
- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate post dose and had neither orthostatic hypotension nor orthostatic heart rate at baseline
- Percentage of patients who had orthostatic hypotension at baseline and did not have orthostatic hypotension post dose

- Percentage of patients who had orthostatic heart rate at baseline and did not have orthostatic heart rate post dose
- Percentage of patients who had both orthostatic hypotension and orthostatic heart rate at baseline and had neither orthostatic hypotension nor orthostatic heart rate post dose

An additional listing of patients who had orthostatic hypotension or orthostatic heart rate post dose will be presented. The listing will include the baseline and post dose heart rate, SBP, and DBP in both the supine and standing positions. The listing will also include the patient's age and whether they were taking a beta blocking agent as a concomitant medication. Patients should be considered to be taking a beta blocking agent if they are taking any of the following at C1D1:

Acebutolol, Atenolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Celiprolol, Esmolol, Labetalol, Levobunolol, Metipranolol, Metoprolol, Nadolol, Nebivolol, Oxprenolol, Penbutolol, Pindolol, Propranolol, Sotalol, Timolol

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

5.10.5 Disseminated Intravascular Coagulation (DIC) and PT/PTT

Data from the DIC panel at screening and prothrombin/partial thromboplastin times will be presented in separate by-patient listings.

5.10.6 Echocardiograms

Echocardiogram results (e.g. LVEF) will be presented in by-patient listing.

5.10.7 Urine Safety Assessment

The urine safety lab data will be presented in by-patient listings, where directly measured urine safety lab tests, the corresponding serum lab tests (serum creatinine, serum albumin, and serum phosphate), and the derived lab quantities mentioned below will be included:

1. Ratio of Urine Albumin/ Urine Creatinine

$$\text{Urine Albumin/Urine - Cr (mg/g)} = \frac{\text{urine albumin}[\mu g/ml]}{\text{urine creatinine}[mg/dL]} \times 100$$

2. Fractional Excretion of Phosphate (FRAC-PO4)

$$\text{FRAC - PO4} = \frac{[(\text{urine phosphate[mg/dL]}) \times (\text{serum creatinine[}\mu\text{mol/L]} / 88.4)]}{[(\text{urine creatinine[mg/dL]}) \times (\text{serum phosphate[mmol/L]} / 0.3229)]} \times 100$$

5.10.8 Pregnancy Test

Pregnancy test result will also be presented in a by-patient listing.

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

There is no change made to the planned analysis from the protocol.

Reference materials for this statistical plan include Clinical Study Protocol P1012 Amendment 3 (Mar 2017)

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.1 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Patient populations are defined in Section 2.

Baseline values are defined as in Section 5.4.2.

Treatment emergent AEs are defined as in Section 5.10.1.1.

8. REFERENCES

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