STATISTICAL ANAYSIS PLAN

NCT Number: NCT03814005

Study Title: A Phase 1/1b Study of Pevonedistat in Combination With Select Standard of Care Agents in Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, Acute Myelogenous Leukemia, or Advanced Solid Tumors With Severe Renal Impairment or Mild or Moderate Hepatic Impairment

Study Number: Pevonedistat-1016

SAP Version and Date:

Version 4.0: 23-February-2022

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Pevonedistat Plus Select Standard of Care Agents Administered in Cancer Patients With Renal or Hepatic Impairment

PHASE 1/1b

Version**:** 4.0

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Prepared by:

[redacted]

[redacted], Statistical and Quantitative Sciences

Based on:

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1.1 Approval Signatures

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Approvals:

[redacted] PhD [redacted] Statistical and Quantitative Sciences	Date

2.0 TABLE OF CONTENTS

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{τ}	area under plasma concentration-time curve over dosing interval
BDC	bile in bile duct–cannulated
BSA	body surface area
BUN	blood urea nitrogen
CDLs	cullin-dependent ubiquitin E3 ligases
CL	total clearance
CMML	chronic myelomonocytic leukemia
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
eCRF	electronic case report form
CR	complete response/remission
CrCL	creatinine clearance
CRO	contract research organization
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELN	European Leukemia Net
EOS	end of study
ET	early termination
FDA	[United States] Food and Drug Administration
f_u	fraction of unbound drug in plasma
FSH	follicle stimulating hormone
GFR	glomerular filtration rate
HI	hematologic improvement
HLT	High level term
HLGT	High level group term
HMA	hypomethylating agents
HR MDS	higher-risk myelodysplastic syndrome
ICF	informed consent form
IPSS-R	Revised International Prognostic Scoring System
IRT	interactive response technology
IV	Intravenous (ly)
LLQ	lower limit of quantification
MDRD	Modification of Diet in Renal Disease
MRT	mean residence time
MTD	Maximum tolerated dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease

PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial remission
PS	performance status
PT	preferred term
PTE	pretreatment events
QTc	prolonged rate corrected
RAEB-	refractory anemia with excess blasts
RBC	red blood cells
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SOE	schedule of events
SC	Subcutaneous(ly)
SOC	system organ class
std dev	standard deviation
$t_{1/2z}$	terminal disposition phase half-life
TAD	time after dosing
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of maximum observed concentration
TRM	treatment-related mortality
ULN	upper limit of the normal range
US	United States
USPI	US Prescribing Information
V_{ss}	volume of distribution at steady-state
WBC	white blood cell
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives (Part A) are as follows:

- To characterize the PK of pevonedistat in patients with severe renal impairment.
- To characterize the PK of pevonedistat in patients with mild hepatic impairment.
- To characterize the PK of pevonedistat in patients with moderate hepatic impairment.

4.2 Secondary Objectives

The secondary objectives (Part A and Part B) are as follows:

- To evaluate disease response in patients with severe renal impairment or mild or moderate hepatic impairment that may be observed in the combination of pevonedistat with chemotherapy (azacitidine, docetaxel, or carboplatin plus paclitaxel).
- To characterize the PK of pevonedistat and azacitidine in the combination setting in patients with hematologic malignancies and severe renal impairment or mild or moderate hepatic impairment.
- To characterize the PK of pevonedistat in combination with docetaxel or carboplatin plus paclitaxel in patients with advanced solid tumors and severe renal impairment or mild or moderate hepatic impairment.

4.3 Additional Objectives

The safety objectives (Part A and Part B) are as follows:

- To evaluate the safety of pevonedistat following a single dose, or in combination with chemotherapy (azacitidine, docetaxel, or carboplatin plus paclitaxel), in patients with normal organ function and in patients with organ impairment.

4.4 Study Design

This study is an open-label, multicenter, phase 1/1b, 2-part study of pevonedistat plus select standard of care (SOC) agents in adult patients with hematologic malignancies (higher-risk myelodysplastic syndromes [HR MDS], higher-risk chronic myelomonocytic leukemia [HR CMML], acute myelogenous leukemia [AML]) or solid tumors with various degrees of renal or hepatic function. Eligible patients will include those with relapsed/refractory MDS, non-proliferative CMML, AML, and metastatic or advanced solid tumors for whom treatment with pevonedistat and SOC agents is appropriate. Patients with previously untreated hematologic malignancies not suitable for induction therapy will also be eligible for enrollment. The study has been designed to characterize the PK and assess the safety of pevonedistat in combination with SOC agents in patients with hematologic malignancies or solid tumors who also have severe renal impairment or mild or moderate hepatic impairment. Patients will be assigned to 1 of the 4

study arms based on their renal and/or hepatic function: normal renal and hepatic function (Control Arm), severe renal impairment (Renal Arm), mild hepatic impairment (Mild Hepatic Arm), and moderate hepatic impairment (Moderate Hepatic Arm).

It is expected that approximately 42 patients will be enrolled in this study. Part A of the study will be a single-agent pevonedistat PK assessment, followed by Part B treatment with pevonedistat in combination with SOC agents (azacitidine, docetaxel, or carboplatin plus paclitaxel).

Once enrolled into the study, all eligible patients will be administered a single dose of pevonedistat 20 mg/m^2 via approximately 1-hour intravenous (IV) infusion on Day 1 of Part A. Plasma PK samples will be collected at a series of predetermined time points up to 72 hours following the single dose of pevonedistat. There will be an approximate 4- to 7-day washout period before the start of Part B. The schedules of events and study schema for the study are provided in Appendix A and Appendix B, respectively.

After completion of Part A, all patients will have the opportunity to continue into Part B of the study.

In Part B, patients with hematologic malignancies may receive pevonedistat on Days 1, 3, and 5 in combination with azacitidine on Days 1 through 5, 8, and 9 in 28-day cycles. During Cycle 1 of Part B, plasma and urine PK samples for measurement of both pevonedistat and azacitidine will be collected at predetermined time points or intervals on Day 3. Plasma PK samples for measurement of pevonedistat will also be collected on Days 4 and 5 of Cycle 1.

Patients with advanced solid tumors may receive pevonedistat in combination with docetaxel or carboplatin plus paclitaxel on Day 1 and pevonedistat alone on Days 3 and 5 in 21-day cycles. During Cycle 1 of Part B, plasma PK samples for measurement of pevonedistat will be collected on Days 3, 4, and 5.

The schedule of sample collection for PK assessments is provided in Appendix A.

Following sponsor and investigator discussion of safety data from Cycle 1, patients in the organ impairment arms who tolerate pevonedistat well at a low starting dose may be eligible for intrapatient dose escalation of pevonedistat starting in Cycle 2 of Part B or soon thereafter. Patients who tolerate treatment well at low starting doses of SOC agents may also be eligible for intrapatient dose escalation of those agents, per USPI/SmPC recommendations.

Details for dosing, study drug administration, and intrapatient dose escalation are provided in Section 8.1 of the protocol.

Patients may continue to receive a combination treatment with pevonedistat in 28-day cycles (in combination with azacitidine) or in 21-day cycles (in combination with docetaxel or carboplatin plus paclitaxel) in Part B until they experience symptomatic deterioration or disease progression, treatment is discontinued for another reason, or until the study is stopped by the sponsor.

Treatment with the study drug will be discontinued early if a patient experiences study drug-related toxicity. Patients may discontinue therapy at any time. Patients will attend the end of

study (EOS)/early termination (ET) visit 30 (+10) days after receiving their last dose of study drug or before the start of subsequent antineoplastic therapy, if that occurs sooner.

Adverse events (AEs) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) will be assessed, and electrocardiograms (ECGs), clinical laboratory values (with select chemistry panel during Part B), 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 5.0, effective date 27 November 2017 [1]. Dose modification guidelines are presented in Section 8.3 of the protocol.

Measures of disease response (complete response [CR] or partial response [PR] for AML and solid tumors; CR, PR, or hepatic improvement [HI] for MDS and CMML), including response rate and duration of response, will be based on the investigator's assessment (Part B only).

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints are as follows:

- Area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) following a single dose of pevonedistat in patients with normal renal and hepatic function, severe renal impairment, or mild or moderate hepatic impairment.
- Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{last}) following a single dose of pevonedistat in patients with normal renal and hepatic function, severe renal impairment, or mild or moderate hepatic impairment.
- Maximum observed plasma concentration (C_{max}) of pevonedistat following a single dose of pevonedistat in patients with normal renal and hepatic function, severe renal impairment, or mild or moderate hepatic impairment.

5.2 Secondary Endpoints

The secondary endpoints are as follows:

- $t_{1/2z}$ of pevonedistat following single- and multiple-dose administration.
- C_{max} of pevonedistat and C_{max} of azacitidine following multiple-dose administration.
- Fraction of unbound drug in plasma (f_u) of pevonedistat.
- Time of first occurrence of maximum observed concentration (T_{max}) of azacitidine following multiple-dose administration.
- $t_{1/2z}$ of azacitidine following multiple-dose administration.

- Area under the concentration-time curve from time zero to the end of the dosing interval (AUC_τ) of pevonedistat and azacitidine following multiple-dose administration.
- Clearance (CL) of pevonedistat and apparent clearance (CL/F) of azacitidine.
- Renal clearance (CL_R) of pevonedistat and azacitidine.
- Volume of distribution at steady-state (V_{ss}) of pevonedistat and apparent V_{ss}/F of azacitidine.
- Measures of disease response, including response rate and duration of response, based on the investigator's assessment (Part B only) using the following responses for each disease type:
  - CR, CRi, or PR for AML.
  - CR, PR, or HI for MDS and CMML.
  - CR or PR in patients with solid tumors using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.

5.3 Exploratory Endpoints

None.

5.4 Safety Endpoints

The safety endpoints are:

- AEs, SAEs, assessments of clinical laboratory values, vital signs measurements, and ECOG PS.

6.0 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the number of patients required to adequately characterize the PK of pevonedistat in the impaired organ function groups (severe renal impairment or mild or moderate hepatic impairment) in comparison to the control group. Based on these considerations, the expected sample size is approximately 9 for the control group (normal renal and hepatic function) and 9 to 12 patients in each of the 3 organ impairment arms. Patients who are considered non-evaluable may be replaced. The sample size of approximately 9 patients specified as being required for the PK population in each group in Part A is based on typical sample sizes utilized in organ impairment PK studies in cancer patients, rather than on specific statistical considerations. With a sample size of 9 patients per group, if the ratio of geometric means (impaired organ function vs control) of AUC_∞ is X, the associated 90% CI is expected to be (0.688X, 1.45X) based on the %CV in pevonedistat AUC_∞ of 43.8% (Study C15011).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This study is largely descriptive, in that no formal statistical hypothesis testing will be performed for the primary endpoints, i.e., AUC_{∞}, AUC_{last}, C_{max}. Summary tabulations will present 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.

Based on the topline results of the Study Pevonedistat-3001 (Pevo-3001), where the primary endpoint of event-free survival (EFS) was not met, Takeda will not pursue further development of pevonedistat in any indication. Thus, enrollment into this study was discontinued (see Section 7.13).

All the tables that display non-PK information from Part A of the study will be presented by study arm (Control Arm, Renal Impairment Arm and Mild Hepatic Arm), and total, unless specified otherwise. The Moderate Hepatic Arm was planned in the study protocol, but no subject was enrolled. As a result, the moderate hepatic arm will not be presented. In addition, inclusion of patients with solid tumors was planned in the study protocol, but no subject was enrolled. As a result, no solid tumor data will be presented either. Due to the small target sample size in this study, the presentation of the non-PK information in Part B will depend on the characteristics of the patients who continue into Part B. By study arm presentation, similarly to Part A will be displayed.

All the tables that display PK information will be presented by Part A and Part B of the study, study arm, dose level (for Part B only), and total, unless specified otherwise.

All available efficacy and safety data will be included in data listings and tables as needed. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

All statistical analyses will be conducted using SAS® Version 9.2, or higher.

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

Screen failure patients will be grouped and listed.

7.1.1 Study Definition

A patient is considered to be enrolled when the first dose of study drug has been administered. Study start date is defined as the date of first dose of study drug for Part A.

7.1.2 Definition of Study Days

Part A

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

Part B

Study Day 1 is defined as the date on which a patient is administered their first dose of the study drug in Cycle 1.

7.1.3 Definition of Baseline Values

Part A

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration during Part A. For analysis of ECG data, the baseline value is the average of the screening and Part A Day 1 predose value if ECG is collected at both screening and Part A Day 1 predose. If ECG is collected at only one of these two time points, the baseline value takes the value of the one that is collected.

Part B

Similarly, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration during Part B. Since there is no screening visit for Part B, the baseline value for ECG is also the one collected at the time closest to, but prior to, the start of study drug administration during Part B.

7.1.4 Definition of Study Visit Windows

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

7.1.5 Conventions for Missing Adverse Event Dates

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

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

- If the stop date has a year and month, 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 stead.

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 1st day of the month will be imputed.
    - If this imputed date is earlier than the 1st dose date, then the 1st dose date will be used instead.
    - If this imputed 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 imputed date is earlier than the 1st dose date, then the 1st dose date will be used instead.
    - If this imputed 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 Dates

Concomitant medications in the category of general medication are not imputed for the missing start dates. Other concomitant medications, such as anti-cancer therapies with start dates that are completely or partially missing will be analyzed and imputed as follows:

1. If the start date has a month and year but the day is missing, the event will be considered concomitant 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 1st dose of study drug

    and
    - on or before the month and year of the date of the last dose of any study drug plus 28 days for patients with hematologic disease, or the start date of subsequent anticancer therapy, whichever occurs first.
    - For the category of prior anti-cancer therapy, the day is imputed to the 15.
    - For the category of alternate therapy, if year and month are the same as those of treatment end date, the day is imputed as the treatment end date plus one; otherwise, the day is imputed as the 1st day of non-missing concomitant medication start month.
2. If the start date has a year, but the day and month are missing, the event will be considered concomitant if the year of the start date of the event is:
    - On or after the year of the date of the 1st dose of study drug

and

- on or before the year of the date of the last dose of any study drug plus 28 days for patients with hematologic disease, or the start date of subsequent anticancer therapy, whichever occurs first.
- For the category of prior anti-cancer therapy, if the year is the same as that of the 1st dose of study drug, the 15th of January will be used unless it is later than the 1st dose date, in which case the 1st of January will be used; if the year is not the same as that of the 1st dose of study drug, the 15th of June will be used unless other data indicate that the date is earlier.
- For the category of alternate therapy, if year is the same as that of treatment end date, the treatment end date plus one is imputed; otherwise, the month and day is imputed as the 1st of January of non-missing concomitant medication start month.

3. If the start date of an event is completely missing, then the event is assumed to be concomitant and no imputation is applied.

However, if the end date is complete or partially missing, but it is clear that the end date is before the first dose of study drug, the event will not be considered concomitant.

When the start date is complete and is before the first dose, and the concomitant medication is not ongoing but the end date is missing completely or partially, a similar algorithm should be used to assess whether the end date is before the last dose of study drug plus 28 days for patients with hematologic disease to be included.

7.2 Analysis Sets

- **Safety population** will include patients who receive at least 1 dose of study drug. The safety population will be used for all safety analyses.
- **PK population** will include patients who:
  - Complete the protocol-specified pevonedistat dosing and PK assessment in Part A and/or protocol-specified pevonedistat and/or azacitidine dosing and PK assessment in Cycle 1 of Part B.
  - Do not receive any excluded concomitant medications through the completion of Part A.
  - Have sufficient concentration-time data to permit reliable estimation of PK parameters.
- **Response-evaluable population** will include patients who receive at least 1 dose of study drug, have a baseline disease assessment, and have at least 1 postbaseline disease assessment for analyses of response.

7.3 Disposition of Patients

A table of patient disposition data will include the number of patients for the following categories: patients treated (safety population), patients in the PK 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 as well. The percentages in this table will be calculated based on the safety population.

Data concerning patient disposition will be presented in by-patient listings.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using safety population in a descriptive fashion, including sex, age, race, ethnicity, weight, height, body surface area (BSA), baseline disease characteristics, and other parameters as appropriate.

All patient demographic and other baseline characteristics listings will include a flag indicating whether a patient continued to Part B of the study. For patients who continue to Part B a SOC agent will be presented as well.

7.4.1 Demographics

Demographic data will include age at date of informed consent (continuous and by the following categories: 18-64 years, 65-84 years, 85 years and over), sex, ethnicity, race, height, weight, and 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 predose weight can be used.

$$BSA = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$$

A separate table will summarize the number and percentage of the patients by region, country and site.

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

7.4.2 Baseline Characteristics

Baseline disease characteristics will be summarized using safety population for MDS/CMML, and AML patients separately. Baseline disease characteristics for MDS/CMML patients will include disease type (de novo MDS/CMML, secondary MDS/CMML), with disease subtype to be summarized for secondary MDS/CMML, months from initial diagnosis, French-American-British category, World Health Organization (WHO) classification and Revised International Prognostic Scoring System (IPSS-R) category. Baseline disease characteristic for AML patients will include disease type (de novo AML and secondary AML), with disease subtype to be summarized for secondary AML, months from initial diagnosis, revised WHO classification, and evidence of extramedullary disease.

Separate by-patient listings will also be presented for baseline disease characteristics and ECOG performance status.

Separate by-patient listings will also be presented for prior therapies and prior transplants.

A separate table will summarize the results of the bone marrow aspirate samples taken at screening for MDS/CMML or AML patients. This will include myeloid to erythroid ratio, myeloblast percentage, cytogenetic abnormalities identified, cell maturing status, and presence of auer rods. Baseline bone marrow aspirate will also be presented in by-patient listings.

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

MDS/CMML patients will be classified and presented in a separate table by five cytogenetic risk groups (Very Good, Good, Intermediate, Poor, and Very Poor) using their cytogenetic results collected at screening based on IPSS-R criteria. The cytogenetic risk classification results will also be included in a by-patient listing.

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

7.5 Medical History

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

7.6 Concomitant Medications

All concomitant medications will be mapped to preferred terms according to the WHO drug dictionary. The number and percentage of patients in the safety population taking concomitant medications will be tabulated by ATC classification and WHO drug generic term and presented for Part A and Part B. Hydroxyurea and hydration usage 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. In addition, a listing will be generated for patients who require hydration as a concomitant medication during the study to display transfusion trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+) for all patients by study arm, disease type and SOC.

7.7 Study Drug Exposure and Compliance

Study drug exposure of pevonedistat in Part A, and pevonedistat as well as azacitidine in Part B will be presented for safety population by-patient listings separately. The extent of exposure to pevonedistat and compliance with pevonedistat and azacitidine dosing requirements will be presented for Part B of the study only by tables and by-patient listings respectively. The extent of exposure to pevonedistat will be based on the number of cycles. Patients will be considered to have been treated for a cycle if they received at least one dose of pevonedistat during that cycle.

For pevonedistat, Percent Dosing Intensity will be calculated using the following equations for Daily Expected Dose (mg), Daily Prepared Dose (mg), and Daily Dose Received (mg):

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

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

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

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:

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

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

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

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 pevonedistat and each SOC separately. The formulas for dosing intensity for SOC agents appear below.

For each SOC agent, the extent of exposure will be presented in a similar manner as pevonedistat. A separate column will be generated for each dose level of pevonedistat, and the number of cycles of SOC agent administered will be summarized.

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

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

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

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

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

The actions on study drugs (Dose Held, Dose Missed, Dose Reduced, Dose Interrupted, Dose Delayed, Dose Incomplete, or Discontinued) will be summarized for Part B by dose level for pevonedistat and azacitidine separately. Data will be summarized for Cycle 1 only as well as all cycles combined. A patient will be counted only once for each type of action.

7.8 Efficacy Analysis

Efficacy measures will include disease response and duration of disease response. Efficacy analysis will be based on response-evaluable population and will be descriptive.

Disease response in AML will be based on the overall response rate (ORR) (CR + CRi + PR) using the Revised Recommendations of the International Working Group (IWG) for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in AML [5].

Disease response in MDS/CMML patients will be based on the best overall response (CR + PR + HI) as determined by the investigator using the revised IWG response criteria for MDS (detailed in Appendix J of the protocol) [6].

The duration of response will be defined in all patients with disease response as the time between the first documentation of response and the first documentation of progressive disease (PD) or death if no prior PD is documented. Responders without disease progression will be censored at the last clinical assessment of response.

For the disease response (CR + CRi + PR + HI), AML patients and MDS/CMML patients will be combined and the number of patients and percentage will be presented by study arm, and total.

The duration of response (in months) and time to first response (in months) will also be presented. 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.

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

7.8.1 Primary Efficacy Endpoint(s)

Not applicable for this study.

7.8.2 Secondary Efficacy Endpoint(s)

- CR, CRi, or PR for AML.
- CR, PR, or HI for MDS and CMML.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable for this study.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Individual and mean pevonedistat plasma concentration-time data following a single dose of pevonedistat during the PK assessment in Part A will be plotted and listed by study arm. Individual and mean pevonedistat and/or azacitidine plasma concentration-time data following

multiple-dose administration during Cycle 1 of Part B will be plotted and listed by study arm and by dose levels. Plasma pevonedistat and/or azacitidine PK parameters for each patient will be calculated using noncompartmental analysis methods. Unbound values of pevonedistat C_{max}, AUC_{last}, AUC_{∞} and AUC_{τ} in individual patients will be calculated as the product of the patient's pevonedistat f_u and the total values of C_{max}, AUC_{last}, AUC_{∞} and AUC_{τ}, respectively. Descriptive statistics will be presented for pevonedistat PK parameters (C_{max}, AUC_{last}, AUC_{∞}, AUC_{τ}, CL, $t_{1/2z}$, CL_R, f_u, $V_{ss,}$ and unbound values of C_{max}, AUC_{last}, AUC_{∞} and AUC_{τ}) by study arm and dose levels. Descriptive statistics will be presented for azacitidine PK parameters (C_{max}, T_{max}, AUC_{τ}, CL/F, $t_{1/2z}$, $CL_{R,}$ V_{ss} by study arm and dose levels.

The analysis for the effects of organ impairment on pevonedistat PK will be based on unbound pevonedistat plasma exposure (AUCs) following a single dose of pevonedistat in Part A. To assess the effects of severe renal impairment or mild hepatic impairment on pevonedistat PK (unbound AUC_{last} and AUC_{∞}), an analysis of variance (ANOVA) on the natural log-transformed PK parameters will be performed for severe renal impairment (Renal Arm) versus the normal group (Control Arm), and mild hepatic impairment (Mild Hepatic Arm) versus the normal group (Control Arm). The ANOVA results will be used to estimate the ratios of least squares geometric means (severe renal impairment vs normal, and mild hepatic impairment vs normal) and corresponding 90% CIs for pevonedistat unbound AUC. The PK population will be used for these analyses.

Individual concentration-time data of pevonedistat administered alone or in combination with azacitidine will be analyzed by noncompartmental methods using a validated version of Phoenix® WinNonlin® (version 6.3 or higher, Pharsight Corporation, Cary, NC).

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_{48}	Area under the plasma concentration-time curve from time zero to 48 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	$ln(2) / lambda_z$
CL or CL/F	Total clearance	Dose / AUC_{∞} after single dosing or dose / AUC_{last} after multiple dosing
V_{ss} or V_{ss}/F	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 $lambda_z$, $t_{1/2z}$, 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) and individual plasma PK parameters will be listed by patient ID and summarized descriptively by study arm, dose levels and study day (Day 1 or Day 5 up to 48 hours, Cycle 1).

Summary statistics (N, arithmetic mean, standard deviation, geometric mean [where appropriate], coefficient of variation [CV], median, minimum, and maximum) will be calculated as deemed appropriate.

For each study arm, 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 study arm, dose level and study day using linear and semi-logarithmic scales for overall population respectively as deemed appropriate (or as data permit). Box plots of pevonedistat dose-normalized AUCs and C_{max} on Day 1 and Day 5, Cycle 1 will be provided by study arm and total as permitted by data.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

A safety analysis will be conducted separately for Part A and Part B. The safety population will be used for the safety analysis. Safety will be evaluated based on the incidence of AEs, severity

and type of AEs, incidence of DLTs, and by changes from baseline in the patient's vital signs, weight, clinical laboratory values, and ECGs.

7.11.1 Adverse Events

7.11.1.1 Adverse Events

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for the purpose of summarization. TEAE 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 according to the MedDRA by system organ class, high level terms (HLT) and preferred terms (PT) and will include the following categories:

- TEAEs
- Drug-related TEAEs
- 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 serious AEs (SAEs)
- Treatment-emergent drug-related SAEs
- Treatment-emergent AEs that require dose modification
- Non-serious TEAEs (>5% in any arm)

Patients with the same AE more than once will have that event counted only once within each body system, once within each HLT, and once within each PT.

Treatment-emergent AEs (TEAE) will be tabulated by system organ class, HLT, PT, and highest intensity.

A separate table for non-serious TEAEs which occur in >5% of the patients in one study arm will be tabulated by system organ class, PT, study arm and total. In addition to the number and percentage of the patients, the number of events will be presented in this table.

All TEAEs categories will be analyzed by study arm and total. All AEs will also be reported in by-patient listings by study arm, disease type and SOC.

A TEAE in Part A is defined as any AE that occurs after administration of the single dose of study drug in Part A and up through 30 days after the single dose of study drug in Part A for patients who do not continue into Part B; or up through Part B Cycle 1 Day 1 (predose) for patients who continue into Part B.

A TEAE in Part B is defined as any AE that occurs after administration of the first dose of study drug in Part B and up through 30 days after the last dose of study drug in Part B.

7.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment-emergent SAE will be summarized by system organ class, HLT, PT, study arm, and total. A similar table will be presented for treatment-emergent drug-related SAEs.

A separate table with the number of SAEs in addition to the number and percentage of patients experiencing SAEs will be summarized by system organ class, PT, study arm, and total.

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 events occurring within a day of first dosing (C1D1) with grade 2 or higher SAEs will also be generated.

7.11.1.3 Deaths

A by-patient listing of the deaths will be presented for all patients by study arm, disease type and SOC. 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.

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

A by-patient listing of TEAEs resulting in discontinuation of study drug will be presented for all patients by study arm, disease type and SOC. All TEAEs resulting in discontinuation of study drug occurring on-study and during follow-up will be displayed.

7.11.1.5 Hemorrhages

By-patient line listing for patients who experienced ANY GRADE TEAE of Hemorrhages (defined by SMQ Hemorrhages, broad and narrow terms) and Thrombocytopenia/Platelet Count Decreased will be provided by study arm, disease type and SOC.

7.11.1.6 Acute Renal Failure Events

A listing of treatment-emergent acute renal failure events will be generated for all patients by study arm, disease type and SOC. The corresponding PTs are within the Acute renal failure SMQ, broad and narrow terms.

7.11.1.7 Liver Function Test (LFT) Elevations

A listing of treatment-emergent LFT elevation events will be generated for all patients by study arm, disease type and SOC. The corresponding PTs, HLT and SMQ are listed as below:

- Acute hepatic failure (PT)
- Drug-induced liver injury (SMQ)
- Hepatic encephalopathy (PT)
- Liver function analyses (HLT)
- Liver injury (PT)
- Blood alkaline phosphatase abnormal

- Hepatocellular injury (PT)
- Hepatotoxicity (PT)
- Hyperbilirubinaemia (PT)
- Hypertransaminasaemia (PT)
- Blood alkaline phosphatase increased (PT)
- Hepatic function abnormal (PT)

7.11.1.8 Tachycardia Events

A listing of treatment-emergent tachycardia events will be generated for all patients by study arm, disease type and SOC. The corresponding PTs are listed as below:

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

7.11.1.9 Hypotension

A listing of treatment-emergent hypotension events will be generated for all patients. Severity and causality will be indicated for all patients by study arm, disease type and SOC. The corresponding PTs 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
- Diastolic hypotension
- Hypotension
- Orthostatic hypotension

7.11.1.10 Anemia

A listing of treatment-emergent anemia events will also be generated for all patients. Severity and causality will be indicated for all patients by study arm, disease type and SOC. The corresponding PTs are listed as below:

- Anaemia of chronic disease
- Anaemia of malignant disease
- Anaemia
- Red blood cell count abnormal
- Haematocrit abnormal
- Haematocrit decreased
- Hemoglobin abnormal
- Hemoglobin decreased

- Red blood cell count decreased
- Mean cell hemoglobin decreased

7.11.1.11 Neutropenia

A listing of treatment-emergent neutropenia will also be generated for all patients. Severity and causality will be indicated for all patients by study arm, disease type and SOC. The corresponding PTs are listed as below:

- Agranulocytosis
- Granulocyte count decreased
- Band neutrophil count decreased
- Band neutrophil percentage decreased
- Leukopenia
- Febrile neutropenia
- Neutropenia
- Neutropenic infection
- Neutropenic sepsis
- Neutrophil count abnormal
- Neutrophil count decreased
- White blood cell count abnormal
- White blood cell count decreased
- Neutrophil percentage abnormal
- Neutrophil percentage decreased

By-patient line listing for patients who experienced ANY GRADE TEAE of Infections (defined by system organ class Infections and infestations, or High Level Group Term [HLGT] Respiratory Tract Infections, or HLT Lower Respiratory Tract Inflammatory and Immunologic Conditions) and Febrile neutropenia (defined by PT Febrile neutropenia) will be generated. The listing will include: patient ID, study arm, 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 who experienced ANY GRADE TEAEs of Infections (defined by system organ class Infections and infestations, or HLGT Respiratory Tract Infections, or HLT Lower Respiratory Tract Inflammatory and Immunologic Conditions) and Neutropenia (defined by PT Neutropenia, PT Neutrophil Count Decreased, PT White Cell Count Decreased) will be generated. The listing will include: patient ID, study arm, 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).

7.11.1.12 Transfusion

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

7.11.1.13 Dose Modifications due to LFT Abnormalities

A listing will be generated for patients who require dose modification due to LFT abnormalities [defined by TEAEs included in section 7.11.1.7 (LFT elevations)] during the study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+) for all patients by study arm, disease type and SOC.

7.11.1.14 Dose Modifications due to Renal Abnormalities

A listing will be generated for patients who require dose modification due to renal abnormalities [as defined by the TEAEs listed in section 7.11.1.6 (Acute renal failure SMQ)] during the study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+) for all patients by study arm, disease type and SOC.

7.11.1.15 Dose Modifications due to Myelosuppression

A listing will be generated for patients who require dose modification due to myelosuppression [defined by the TEAEs listed in sections 7.11.1.10 (Anemia), 7.11.1.11 (Neutropenia), plus 2 additional PTs of Thrombocytopenia and Platelet count decreased)] during the study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+) for all patients by study arm, disease type and SOC.

7.11.1.16 Overall Summary

The number and percentage of patients who experience any of the following will be summarized by study arm, and total.

- Any TEAE (including separate summaries of maximum toxicity grade experienced (Grade 1 to Grade 5)
- Drug-related TEAE (including separate summaries of maximum toxicity grade experienced (Grade 1 to Grade 5)
- Serious TEAE
- Drug related serious TEAE
- TEAE that required dose modification

7.11.2 Dose Limiting Toxicities (DLTs)

A by-patient listing of DLTs will be presented for all patients by study arm, disease type and SOC.

7.11.3 Clinical Laboratory Evaluations

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 (e.g., 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.

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. Clinical laboratory evaluations all have been done in local laboratories for P1016 study.

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 presented for Part A and Part B separately, summarized according to the scheduled sample collection time point. Given that lab tests are done for pre-dose and 4-hour post-dose for Part A, the shift from baseline to worst post-baseline be presented for the whole period of the study. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

All the tables and graphs will be displayed for safety population and will be presented by study arm and total. 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. The following graphical displays will be used to show changes in laboratory measures over time:

1. Box graphs of mean laboratory values over time for key laboratory parameters (see table below).

Panel	Test	CTCAE Shift Table	Box Graphs		Summary Tables
Chemistry	Albumin	X	X		
	ALT	X	X		X
	AST	X	X		X
	Alkaline Phosphatase	X	X		
	Carbon Dioxide		X		
	Direct Bilirubin	X	X		
	Total Bilirubin	X	X		X
	Blood urea nitrogen		X		
	Calcium	X	X		
	Chloride		X		
	Creatinine	X	X		
	Creatinine Clearance		X		X
	Glucose	X	X		
	Lactate dehydrogenase (LDH)		X		
	Magnesium	X	X		
	Phosphate	X	X		X
	Potassium	X	X		X
	Sodium	X	X		

Panel	Test	CTCAE Shift Table	Box Graphs		Summary Tables
	Urate	X	X		
Hematology	Platelets	X	X		X
	Hemoglobin	X	X		
	Hematocrit		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)

The following Modification in Renal Disease Study (MDRD) equation will be used to calculate eGFR (mdrd.com):

eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr, std})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American).

All chemistry and hematology lab data will also be presented in by-patient listings for all patients by study arm, disease type and SOC.

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

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

- >3x-, >5x-, >10x-, and >20x ULN elevations of AST and/or ALT;
- Any elevations of bilirubin: elevated total bilirubin to ≥2x ULN;
- Any elevations of alkaline phosphatase >1.5x ULN;
- Elevation of aminotransferase (>3x ULN) accompanied by elevated bilirubin (>1.5x ULN, >2x ULN); and

- Potential Hy's law cases. The Sponsor qualifies these as "potential" cases, since a bona fide case definition requires that no other cause nor other drug has been shown to be causative than the test article. In some advanced cases with more cholestasis, the alkaline phosphatase may be >2x ULN.

7.11.4 Vital Signs

Tables for vital signs data will be displayed for safety population and will be presented for Part A and Part B separately by study arm and total.

Summary table of weight and percent change from baseline in weight over time will be provided. Tables will be used to show changes in vital sign parameters, including oral temperature, heart rate, and systolic and diastolic blood pressure, over time.

Vital sign data will also be presented in a by-patient listing for all patients, by study arm, disease type, and SOC.

7.11.5 12-Lead ECGs

A 12-lead electrocardiogram (ECG) will be summarized over each time point, i.e., screening, pre-treatment Day 1 part B, end of the study. QTc intervals (QTcF and QTcB) will be derived by the Sponsor using the following formulas.

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

ECG findings will also be presented in by-patient listings separately for screening, pre-treatment Day 1 part B, end of the study. Shift tables of the change from baseline to the post baseline worst will be generated for the safety population and will be presented by study arm and total.

ECG Parameter	Abnormal values
QTcF and QTcB	New absolute values >450, >480 and >500
	Changes from baseline >30 and >60
HR	Decrease from baseline >25% and to a HR < 50
	Increase from baseline >25% and to a HR > 100
PR	Increase from baseline >25% and to a value >200
ECG Parameter	Abnormal values
QRS	Increase from baseline >25% and to a value >110

7.11.6 Safety Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG shifts from baseline to post-baseline assessment over time will be tabulated for the whole study period for the safety population and will be presented by study arm and total.

A listing will be presented for ECOG performance status for safety population, ordered by study arm, disease type, and SOC.

7.11.7 Protocol Deviations

A listing will be presented for significant protocol deviation for safety population, ordered by study arm, disease type, and SOC.

7.12 Interim Analysis

No interim analysis is planned.

7.13 Changes in the Statistical Analysis Plan

The rationale of the SAP amendment is to decrease the scope of analysis due to the small number of enrolled subjects. The enrollment was discontinued after the pivotal Pevonedistat phase 3 study (P3001) did not meet the primary efficacy endpoint, resulting in discontinuation of clinical development of Pevonedistat. As a consequence, further enrollment into P1016 was discontinued, leaving 17 subjected enrolled in total in this study. The main changes include:

- Removal of all analyses of patients with moderate hepatic impairment because these is no patient enrolled in the moderate hepatic arm.
- Removal of all analyses of patients with solid tumors because these is no patient with solid tumors enrolled in the study.
- Some planned tabulations were removed. The events of interest will be captured in listings.

For further details, please refer to Clinical Study Protocol P1016 Amendment 04 (27 May 2021).

8.0 REFERENCES

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9.0 APPENDICES

Appendix A Schedule of Events (SOE)

SOE for Part A: Single-Agent Pevonedistat and PK (All Patients)

	Screening [a]	PK Period				EOS/ ET
	Days	Day 1	Day 2	Day 3	Day 4 [b]	
Procedure	**Window**					**(+10 days)**
Informed consent	x					
Inclusion/exclusion criteria [c]	x					
Demographics	x					
Medical history	x					
Complete physical examination	x					x
Symptom-directed physical examination [d]		x [e]				
Height	x					
Weight [f]	x	x [e]				x
Vital signs [g]	x	x				x
ECOG PS	x	x [e]				x
12-lead ECG	x					x
Pregnancy test [h]	x	x [e]				x
Hematology [i]	x	x [e]				x
Coagulation	x					
Complete chemistry panel [j]	x	x [e]				x
Urinalysis [k]	x					x
Pevonedistat IV infusion		x [l]				
Plasma sample for pevonedistat PK (see Table A)		x	x	x	x	
Plasma sample for pevonedistat protein binding (see Table A)		x				
Bone marrow aspiration/biopsy and investigator disease assessment for patients with hematologic malignancies only [m]	x					

Procedure	Screening [a] Days / Window	PK Period Day 1	Day 2	Day 3	Day 4 [b]	EOS/ ET (+10 days)
Tumor assessment for solid tumors by RECIST, version 1.1 [n]	x					x [o]
Monitoring of concomitant medications and procedures	Recorded from the first dose of any study drug through 30 days (+10) days after the last dose of any study drug.					
RBC and platelet transfusion documentation	Recorded from 8 weeks before enrollment through 30 days after the last dose of any study drug.					
AE/SAE reporting	Recorded from the first dose of any study drug through 30 days (+10) days after the last dose of any study drug. AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).					
	SAEs will be reported from signing of the ICF through 30 days after the last dose of any study drug.					

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AML: acute myelogenous leukemia; AST: aspartate aminotransferase; BSA: body surface area; BUN: blood urea nitrogen; CT: computerized tomography; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; eGFR: estimated glomerular filtration rate; EOS: end of study; ET: early termination; ICF: informed consent form; IV: intravenous(ly); MDRD: Modification of Diet in Renal Disease; PK: pharmacokinetic(s); RBC: red blood cells; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SC: subcutaneous(ly); SOE: schedule of events; WBC: white blood cell.

An EOS visit is needed in Part A only if for any reason the patient does not continue into Part B.

[a] Unless otherwise noted, the screening visit must occur within 28 days before the day of the first dose of study drug on Day 1.

[b] Patients may start Part B 4 to 7 days after the pevonedistat dose in Part A.

[c] Confirmation of patient eligibility by the sponsor's project clinician (or designee) is required prior to enrollment. A patient eligibility checklist must be completed and submitted by the investigator for review and approval by the sponsor or designee prior to patient enrollment. For assessment of hepatic function, 2 blood samples (total bilirubin and ALT), will be required before the start of pevonedistat dosing on Day 1. These 2 samples should be obtained at least 48 hours apart, with the latest sample obtained no more than 48 hours before Day 1 and may be taken predose on Day 1. If the total bilirubin and ALT measurements from the 2 samples indicate the same liver function category for the patient (ie, normal, mild, or moderate hepatic impairment), pevonedistat can be administered as scheduled. If the results of the 2 samples indicate different liver function categories, a third sample must be obtained at least 48 hours after the second sample. If the results of the 2 most recent measurements (the second and third) denote the same liver function category, the patient may be enrolled and should receive a single dose of pevonedistat on Day 1 within 48 hours of the third sample. If the second and third measurements indicate different liver function categories, the patient will not be eligible for inclusion in the study. For assessment of renal function, at least 2 blood samples will be collected to determine spot serum creatinine for calculation of the eGFR according to the MDRD equation (see Section 9.4.15.1 of the Protocol). The sampling for spot serum creatinine should be done within 14 days of starting treatment, with the most recent measurement performed within 7 days of starting treatment. The 2 measurements should both meet eligibility requirements based on the MDRD formula. If the 2 eGFR values do not both meet eligibility requirements, a third measurement will be taken and the 2 most recent measurements (the second and third) will be averaged to assess renal function status.

[d] The symptom-directed physical examination will be conducted within 3 days before dosing on Day 1. The symptom-directed physical examination may be performed at other visits during Part A of the study at the discretion of the investigator.

[e] Except for measurement of WBC count, procedures conducted during the screening period that are performed within 24 hours of Day 1 can also be used as the predose Day 1 evaluation and do not need to be repeated. If dosing falls on a Monday, the collection window may be extended to collect samples on a previous Friday, with the exception of the hepatic and renal function assessments.

[f] Weight will be measured during screening and within 3 days before Day 1 dosing for calculating BSA. BSA will be calculated using a standard formula (see example in Appendix H of the Protocol) on Day 1.

[g] Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be obtained at screening. On Day 1, vital signs are to be measured predose (20 minutes [±10 minutes]) before the infusion of pevonedistat, 30 minutes (±10 minutes) after the start of the pevonedistat infusion, and 30 min (±10 minutes) after the completion of the pevonedistat infusion. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection. Vital sign measurements will be taken with the patient in the supine (after 3-5 minutes in this position) or sitting position (after 3-5 minutes in this position). Either oral or axial body temperature may be used, but the same method for measuring body temperature (oral or axial) should be used consistently for the same patient throughout the study.

[h] A serum pregnancy test will be performed for women of childbearing potential at screening and within 3 days before study drug dosing on Day 1. The results from these tests must be available and negative before the first dose of study drug is administered.

[i] Hematology samples will be collected during screening and within 3 days before infusion/administration with study drug on Day 1. Please note: The sample for WBC count must be drawn before dosing on Day 1. For patients with hematologic disease, WBC count must be <50,000/µL before administration of pevonedistat; hydroxyurea may be used to control the level of WBCs to no lower than 10,000/µL while on pevonedistat. An additional sample will be taken on Day 1 at 4 hours after the completion of pevonedistat infusion.

[j] Samples for the full clinical chemistry panel will be collected predose on Day 1. In addition, samples will be taken on Day 1 at 4 hours after the completion of pevonedistat infusion (see Table 9.d in the Protocol).

[k] Urinalysis will be analyzed locally. See Section 9.4.15.1 of the Protocol. for additional details.

[l] All eligible patients will receive a single dose of 20 mg/m^2 pevonedistat via a 1-hour IV infusion on Day 1. Plasma PK samples will be collected at a series of predetermined time points up to 72 hours (Day 4) following the single dose of pevonedistat. There will be no SOC agents or additional pevonedistat dosing in Part A.

[m] At screening and for study eligibility, a bone marrow aspiration and biopsy (performed locally) will be required to assess disease burden, cytogenetics, molecular characterizations, and cellular composition by flow cytometry. A bone marrow biopsy (in addition to bone marrow aspirate) is required only at screening to confirm the diagnosis. However, a bone marrow biopsy may be collected with bone marrow aspirate in accordance with institutional guidelines. If a biopsy was done within 28 days before enrollment, this archival biopsy may be used and does not need to be repeated. If a bone marrow biopsy is not collected routinely per country/institutional guidelines, it is not required.

[n] Radiological imaging (CT scan or magnetic resonance imaging) of chest, abdomen, and pelvis are required as entry criteria for this study to assess the status of the patient's underlying disease. If the patient has had appropriate imaging scans performed within 28 days before the first dose of study drug in Part A, the results of those scans may be used.

[o] An EOS/ET CT scan does not need to be completed/repeated if a scan was performed within the previous 28 days.

Table A Part A: Pevonedistat Plasma PK Sampling Schedule – Pevonedistat Single-Dose PK (All Patients)

Pevonedistat Plasma PK Sample	Day 1	Day 2	Day 3	Day 4
Predose	x [a,c]			
End of pevonedistat infusion	x [b,c]			
30 minutes (± 5 minutes) post infusion of pevonedistat	x [d]			
1 hour (± 15 minutes) post infusion of pevonedistat	x [d]			
2 hours (±20 minutes) post infusion of pevonedistat	x [d]			
3 hours (±20 minutes) post infusion of pevonedistat	x [d]			
4 hours (±30 minutes) post infusion of pevonedistat	x [d]			
6 hours (±30 minutes) post infusion of pevonedistat	x [d]			
8 hours (±30 minutes) post infusion of pevonedistat	x [d]			
24 hours (±1 hour) postdose of pevonedistat		x [e]		
48 hours (±1 hour) postdose of pevonedistat			x [e]	
72 hours (±1 hour) postdose of pevonedistat				x [e]

IV: intravenous(ly); PK: pharmacokinetics.

[a] The predose sample is to be collected within 1 hour before pevonedistat infusion.

[b] The sample is to be collected at the end of pevonedistat infusion (immediately before stopping the IV infusion). The infusion takes approximately 1 hour.

[c] Samples for pevonedistat plasma protein binding measurement should be collected predose and at the end of infusion. The end of infusion sample will be used if bioanalytically feasible. If not feasible, the predose sample will also be used for pevonedistat plasma protein binding measurement.

[d] The time of sample collection is to be based on the time of completion of pevonedistat infusion.

[e] The time of sample collection is to be based on the time of initiation of pevonedistat infusion.

SOE for Part B: Treatment Cycle 1 (28-Day Cycle) Through EOS (Patients with Hematologic Malignancies Only)

		Cycle 1 and Subsequent Cycles (28 days)							
	Day	**Day 1**	**Day 3**	**Day 4**	**Day 5**	**Day 8 [a]**	**Day 15 [a]**	**Day 22**	**EOS/ET**
Procedure	**Window**					**(±1 day)**	**(±3 day)**	**(±3 days)**	**(+10 days) [b]**
Symptom-directed physical examination [c]		x							
Complete physical examination									x
Weight		x [d]							x
Vital signs [e]		x	x		x				x
ECOG PS [f]		x							x
12-lead ECG [g]		x							x
Pregnancy test [h]		x							x
Hematology [i]		x	x		x	x	x	x	x
Complete chemistry panel		x							x
Select chemistry panel [j]			x		x	x	x	x	
Urinalysis [k]		x							x
Plasma sample for pevonedistat PK (Cycle 1 only, see Table B)			x	x	x				
Plasma sample for azacitidine PK (Cycle 1 only, see Table B)			x						
Urine sample for pevonedistat PK (Cycle 1 only, see Table B)			x						
Urine sample for azacitidine PK (Cycle 1 only, see Table B)			x						
Bone marrow aspiration/biopsy and investigator disease assessment	See the Bone Marrow Collection and Assessment Schedule (Table C).								
Pevonedistat IV infusion [l]	Days 1, 3, and 5 of each cycle.								
Azacitidine SC administration [l]	Days 1-5, 8, and 9 of each cycle.								
Monitoring of concomitant medications and procedures	Recorded from the first dose of any study drug through 30 days (+10) days after the last dose of any study drug.								

	Day	Cycle 1 and Subsequent Cycles (28 days)							EOS/ET
		Day 1	Day 3	Day 4	Day 5	Day 8 [a]	Day 15 [a]	Day 22	
Procedure	**Window**					**(±1 day)**	**(±3 day)**	**(±3 days)**	**(+10 days) [b]**
RBC and platelet transfusion documentation	Recorded from 8 weeks before enrollment through 30 days after the last dose of any study drug.								
AE/SAE reporting	Recorded from the first dose of any study drug through 30 days (+10) days after the last dose of any study drug. AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).								
	SAEs will be reported from signing of the ICF through 30 days after the last dose of any study drug.								

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BSA: body surface area; BUN: blood urea nitrogen; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; EOS: end of study; ET: early termination; IV: intravenous(ly); PK: pharmacokinetic(s); RBC: red blood cells; SAE: serious adverse event; SC: subcutaneous(ly); SOE: schedule of events; WBC: white blood cell.

Study completion is defined as completion of study treatment and the EOS visit.

Nonessential protocol visits in Part B that do not require on-site sample collection and assessment may be completed via telemedicine (video or phone conversation between the patient and the treating physician, if allowed per institutional guidelines) in situations where a site visit cannot be conducted, such as in a COVID 19 pandemic. The reason for telemedicine (eg, COVID 19 related) and for the assessments performed are to be captured in the electronic data capture (EDC).

[a] Hematology samples and select chemistry panels will be collected on Days 8 (±1 day) and 15 (±1 day) in Cycle 1 and in any cycle in which intrapatient dose escalation of any study drug occurs.

[b] The EOS/ET visit will occur 30 days (+10 days) after the last dose of study drugs or before the start of subsequent antineoplastic therapy, if that occurs sooner.

[c] The symptom-directed physical examination will be conducted within 3 days before dosing on Day 1 of each treatment cycle. The symptom-directed physical examination may be performed at other visits during the treatment cycle at the discretion of the investigator.

[d] Weight will be measured within 3 days before Day 1 dosing in each cycle, for calculating BSA. BSA will be calculated using a standard formula (see example in Appendix H of the Protocol) on Cycle 1 Day 1, and on Day 1 of subsequent cycles if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

[e] Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected predose (30 minutes [±10 minutes]) before the infusion of pevonedistat and 30 minutes (±10 minutes) after the start of the pevonedistat infusion on Days 1, 3, and 5 of each cycle, at EOS/ET, and as clinically indicated at the discretion of the investigator. On Cycle 1 Day 1, vital signs are to be measured predose (20 minutes [±10 minutes]) before the infusion of pevonedistat, 30 minutes (±10 minutes) after the start of the pevonedistat infusion, and 30 min (±10 minutes) after the completion of the pevonedistat infusion. Vital sign measurements will be taken with the patient in the supine (after 3-5 minutes in this position) or sitting position (after 3-5 minutes in this position). Either oral or axial body temperature may be used, but the same method for measuring body temperature (oral or axial) should be used consistently for the same patient throughout the study.

[f] ECOG PS will be performed within 3 days before the beginning (Day 1) of each treatment cycle and at the EOS/ET visit.

[g] A 12-lead ECG will be performed Day 1 predose of every cycle and at EOS/ET. Predose assessment may be performed up to 3 days in advance if necessary. ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient supine and rested for 5 minutes.

[h] A serum pregnancy test will be performed for women of childbearing potential within 3 days before Day 1 of each cycle and at EOS/ET. The results from these tests must be available and negative before the study drug is administered on Day 1. If the Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

[i] Hematology samples will be collected before infusion with study drug(s) on Days 1, 3, and 5, and on Day 22 of each cycle, and at EOS/ET. Samples may be drawn up to 1 day before dosing. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. Additional collections on Days 8 (±1 day) and 15 (±1 day) will be performed in Cycle 1 **or in any cycle in which study drug dose is escalated.** Please note: The sample for WBC count must be drawn before each dose on Days 1, 3, and 5. WBC count must be <50,000/µL before administration of pevonedistat; hydroxyurea may be used to control the level of WBCs to no lower than 10,000/µL while on pevonedistat.

[j] The select chemistry panel will be collected predose on Days 3 and 5 and on Day 22 of each cycle. For Days 3 and 5, samples may be drawn up to 1 day before dosing. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. Additional collections on Days 8 (±1 day) and 15 (±1 day) will be performed in Cycle 1 **or in any cycle in which study drug dose is escalated.** The select chemistry panel will include the following: BUN, creatinine, total bilirubin, ALP, AST, and ALT.

[k] Urinalysis will be analyzed locally. See Section 9.4.15.1 of the Protocol for additional details.

[l] Following a 4- to 7-day washout period after single-dose pevonedistat administration in Part A, starting on Day 1 patients will receive pevonedistat on Days 1, 3, and 5 in combination with azacitidine on Days 1 through 5, 8, and 9 in 28-day cycles. On Days 1, 3, and 5, when both study drugs are administered, azacitidine will be administered first, followed by pevonedistat. The pevonedistat infusion may be slowed or stopped and restarted for any associated infusion-related reactions. Following sponsor and investigator discussion of the available safety data, patients who tolerate treatment well at the initially assigned dose of pevonedistat may be allowed to increase their dose during Cycle 2 or in subsequent cycles of treatment. Eligible patients may continue to receive treatment in Part B until they experience symptomatic deterioration or disease progression, treatment is discontinued for another reason, or until the study is stopped by the sponsor. See Section 8.0 of the Protocol for details of study drug administration.

Table B Part B: Azacitidine and Pevonedistat Plasma and Urine PK Sampling Schedule in Cycle 1 (Patients with Hematologic Malignancies Only)

Day	Dosing [a]		Azacitidine Plasma PK		Pevonedistat Plasma PK		Urine PK for Azacitidine and Pevonedistat
	Azacitidine	Pevonedistat	Timepoint	Sample	Timepoint	Sample	Timepoint
3	x		Predose	x [b]	Predose [b]	x [b]	Predose [c]
		x (start infusion)	5 minutes (±5 minutes)	x [d]			0–2 hours postdose interval [g]
			15 minutes (±5 minutes)	x [d]			
			30 minutes (±10 minutes)	x [d]			
			45 minutes (±10 minutes)	x [d]			
		x (end infusion)	1 hour (±10 minutes)	x [d,e]	End of pevonedistat infusion	x [e,f]	
			1.5 hours (±10 minutes)	x [d,e]	30 minutes (±5 minutes)	x [e,h]	
			2 hours (±20 minutes)	x [d,e]	1 hour (±15 minutes)	x [e,h]	
			3 hours (±20 minutes)	x [d,e]	2 hours (±20 minutes)	x [e,h]	
			4 hours (±30 minutes)	x [d,e]	3 hours (±30 minutes)	x [e,h]	2-4 hours postdose interval [g]
			5 hours (±30 minutes)	x [d,e]	4 hours (±30 minutes)	x [e,h]	
			7 hours (±30 minutes)	x [d,e]	6 hours (±30 minutes)	x [e,h]	4-6 hours postdose interval [g]
					8 hours (±30 minutes)	x [h]	6–8 hours postdose interval [g]
4					24 hours (±1 hour)	x [i]	
5					48 hours (±1 hour)	x [i,j]	

IV: intravenous; PK: pharmacokinetic(s); SC: subcutaneous(ly).

[a] For days when azacitidine is coadministered with pevonedistat, azacitidine SC will be given first, followed by pevonedistat infusion.

[b] The predose plasma sample is to be collected within 10 minutes before the start of azacitidine administration.

[c] Patients should be asked to void completely in a container approximately 30 minutes before administration of the first dose of study drug. An aliquot of this spot urine specimen will be a predose urine sample. Detailed instructions on the procedure for collection, processing, storage, and shipment of the urine samples will be provided in the Study Manual.

[d] Samples should be collected after azacitidine SC administration.

[e] These samples are collected to measure both azacitidine and pevonedistat plasma concentrations.

[f] The sample is to be collected at the end of pevonedistat infusion (immediately before stopping the IV infusion). The pevonedistat infusion takes approximately 1 hour.

[g] Postdose intervals are based on completion of azacitidine SC administration.

[h] The time of sample collection is to be based on the time of completion of pevonedistat IV infusion on Day 3.

[i] The time of sample collection is to be based on the time of initiation of pevonedistat IV infusion on Day 3.

[j] The sample is to be collected before the combination dose administration on Day 5.

Table C Bone Marrow Collection and Assessment Schedule (Patients with Hematologic Malignancies Only)

Assessment	Screening	Cycle 2 Day 22 (+6 Days)	Cycle 5 (Between Days 15-28)	Cycle 8 (Between Days 15-28)	Cycle 11 (Between Days 15-28)	Subsequent Cycles (Between Days 15-28); *Every 6 Cycles Thereafter*	Relapse
Bone marrow blast count	x [a]	x [b]	x [b]	x [b]	x [b]	x [b]	x
Cytogenetics [c]	x	x	x	x	x	x	x

eCRF: electronic case report form; FISH: fluorescence in situ hybridization.
All samples will be collected and analyzed locally.

[a] At screening and for study eligibility, a bone marrow aspiration and biopsy (performed locally) will be required to assess disease burden, cytogenetics, molecular characterizations, and cellular composition by flow cytometry. A bone marrow biopsy (in addition to bone marrow aspirate) is required only at screening to confirm the diagnosis. However, a bone marrow biopsy may be collected with bone marrow aspirate in accordance with institutional guidelines. If a biopsy was done within 28 days before enrollment, this archival biopsy may be used and does not need to be repeated. If bone marrow biopsy is not collected routinely per country/institutional guidelines, it is not required.

[b] A bone marrow aspirate for blast count (to determine disease response) will be performed on Day 22 (+6 days) of Cycle 2, and between Days 15 and 28 of Cycle 5, Cycle 8, Cycle 11, and then every 6 cycles afterward or otherwise as clinically indicated at the discretion of the investigator. Results must be available before dosing starts in the next cycle.

[c] Cytogenetics analysis will be done at the clinical site: a bone marrow aspirate sample will be tested according to institutional guidelines in a cytogenetics laboratory routinely used by the site. Analyses should be done by karyotype, and by FISH if possible. Results will be collected in the eCRF.

SOE for Part B: Treatment Cycle 1 (21-Day Cycle) Through EOS (Patients with Advanced Solid Tumors Only)

		Cycle 1 and Subsequent Cycles (21 days)						
	Day	**Day 1**	**Day 3**	**Day 4**	**Day 5**	**Day 8 [a]**	**Day 15 [a]**	**EOS/ET**
Procedure	**Window**					**(±3 day)**	**(±3 day)**	**(+10 days) [b]**
Symptom-directed physical examination [c]		x						
Complete physical examination								x
Weight		x [d]						x
Vital signs [e]		x	x		x			x
ECOG PS [f]		x						x
12-lead ECG [g]		x						x
Pregnancy test [h]		x						x
Hematology [i]		x	x		x	x	x	x
Complete chemistry panel		x						x
Select chemistry panel [j]			x		x	x	x	
Urinalysis [k]		x						x
Plasma sample for pevonedistat PK (Cycle 1 only, see Table D)			x	x	x			
Tumor assessment for solid tumors by RECIST, version 1.1 [l]	To be completed within 28 days before dosing in Part B, end of Cycle 2, Cycle 5, and every 6 cycles thereafter.							x
Pevonedistat IV infusion [m]	Days 1, 3, and 5 of each cycle.							
Chemotherapy IV infusion [m]	Day 1 of each cycle.							
Monitoring of concomitant medications and procedures	Recorded from the first dose of any study drug through 30 days (+10) days after the last dose of any study drug.							
RBC and platelet transfusion documentation	Recorded from 8 weeks before enrollment through 30 days after the last dose of any study drug.							
AE/SAE reporting	Recorded from the first dose of any study drug through 30 days (+10) days after the last dose of any study drug. AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).							
	SAEs will be reported from signing of the ICF through 30 days after the last dose of any study drug.							

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BSA: body surface area; BUN: blood urea nitrogen; CT: computerized tomography; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; EOS: end of study; ET: early termination; ICF: informed consent form; IV: intravenous(ly); MRI: magnetic resonance imaging; PK: pharmacokinetic(s); RBC: red blood cells; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SOE: schedule of events

Study completion is defined as completion of study treatment and the EOS visit.

Nonessential protocol visits in Part B that do not require on-site sample collection and assessment may be completed via telemedicine (video or phone conversation between the patient and the treating physician, if allowed per institutional guidelines) in situations where a site visit cannot be conducted, such as in a COVID 19 pandemic. The reason for telemedicine (eg, COVID 19 related) and for the assessments performed are to be captured in the electronic data capture (EDC).

[a] Hematology samples and select chemistry panels will be collected on Days 8 (±1 day) and 15 (±1 day) in Cycle 1 and in any cycle in which intrapatient dose escalation of any study drug occurs.

[b] The EOS/ET visit will occur 30 days (+10 days) after the last dose of study drugs or before the start of subsequent antineoplastic therapy, if that occurs sooner.

[c] The symptom-directed physical examination will be conducted within 3 days before dosing on Day 1 of each treatment cycle. The symptom-directed physical examination may be performed at other visits during the treatment cycle at the discretion of the investigator.

[d] Weight will be measured within 3 days before Day 1 dosing in each cycle, for calculating BSA. BSA will be calculated using a standard formula (see example in Appendix H of the Protocol) on Cycle 1 Day 1, and on Day 1 of subsequent cycles if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

[e] Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected predose (30 minutes [±10 minutes]) before the infusion of pevonedistat and 30 minutes (±10 minutes) after the start of the pevonedistat infusion on Days 1, 3, and 5 of each cycle, at EOS/ET, and as clinically indicated at the discretion of the investigator. On Cycle 1 Day 1, vital signs are to be measured predose (20 minutes [±10 minutes]) before the infusion of pevonedistat, 30 minutes (±10 minutes) after the start of the pevonedistat infusion, and 30 min (±10 minutes) after the completion of the pevonedistat infusion. Vital sign measurements will be taken with the patient in the supine (after 3-5 minutes in this position) or sitting position (after 3-5 minutes in this position). Either oral or axial body temperature may be used, but the same method for measuring body temperature (oral or axial) should be used consistently for the same patient throughout the study.

[f] ECOG PS will be performed within 3 days before the beginning (Day 1) of each treatment cycle and at the EOS/ET visit.

[g] A 12-lead ECG will be performed Day 1 predose of every cycle and at EOS/ET. Predose assessment may be performed up to 3 days in advance if necessary. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient supine and rested for 5 minutes.

[h] A serum pregnancy test will be performed for women of childbearing potential within 3 days before Day 1 of each cycle and at EOS/ET. The results from these tests must be available and negative before the study drug is administered on Day 1. If the Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

[i] Hematology samples will be collected before infusion with study drug(s) on Days 1, 3, and 5, and EOS/ET. Samples may be drawn up to 1 day before dosing. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. Additional collections on Days 8 (±1 day) and 15 (±1 day) will be performed in Cycle 1 **or in any cycle in which study drug dose is escalated.**

[j] The select chemistry panel will be collected predose on Days 3 and 5 and will include the following: BUN, creatinine, total bilirubin, ALP, AST, and ALT. On Days 3 and 5 samples may be drawn up to 1 day before dosing. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. Additional collections on Days 8 (±1 day) and 15 (±1 day) will be performed in Cycle 1 **or in any cycle in which study drug dose is escalated.**

[k] Urinalysis will be analyzed locally. See Section 9.4.15.1 of the Protocol for additional details.

[l] Tumor assessment will be performed before the start of the study and at the completion of Cycle 2, Cycle 5, and every 6 cycles thereafter in Part B. Patients will undergo CT (with IV contrast, except for patients with an allergy to contrast agents), MRI, x-ray, and/or bone scanning to monitor and assess disease progression. If the anatomic region cannot

be adequately imaged by CT, MRI may be used instead; see Section 9.4.17.2 of the Protocol. An EOS/ET CT scan does not need to be completed/repeated if a scan was performed within the previous 28 days. Response will be determined according to RECIST version 1.1.

[m] The investigator will select which chemotherapy (docetaxel or carboplatin plus paclitaxel) that each patient will receive in combination with pevonedistat. Following a 4- to 7-day washout period after single-dose pevonedistat administration in Part A, starting on Cycle 1 Day 1, patients will receive pevonedistat and chemotherapy agents on Day 1 and pevonedistat alone on Days 3 and 5 in 21-day cycles. The infusion of pevonedistat may be slowed or stopped and restarted for any associated infusion-related reactions. Following sponsor and investigator discussion of the available safety data, patients who tolerate treatment well at the initially assigned dose of pevonedistat may be allowed to increase their dose during Cycle 2 or in subsequent cycles of treatment. The chemotherapeutic agent may be dose reduced because of toxicities in accordance with Section 8.3.2.3 of the Protocol. See Section 8.0 of the Protocol for the details of study drug administration.

Table D Part B: Pevonedistat Plasma PK Sampling Schedule in Cycle 1 (Patients with Advanced Solid Tumors)

Day	Dosing	Pevonedistat Plasma PK	
	Pevonedistat	Timepoint	Sample
3		Predose [a]	x [a]
	x (start infusion)		
	x (end infusion)	End of pevonedistat infusion	x [b]
		30 minutes (±5 minutes)	x [c]
		1 hour (±15 minutes)	x [c]
		2 hours (±20 minutes)	x [c]
		3 hours (±30 minutes)	x [c]
		4 hours (±30 minutes)	x [c]
		6 hours (±30 minutes)	x [c]
		8 hours (±30 minutes)	x [c]
4		24 hours (±1 hour)	x [d]
5		48 hours (±1 hour)	x [d]

IV: intravenous; PK: pharmacokinetic(s).

[a] The predose plasma sample is to be collected within 10 minutes before the start of pevonedistat infusion.

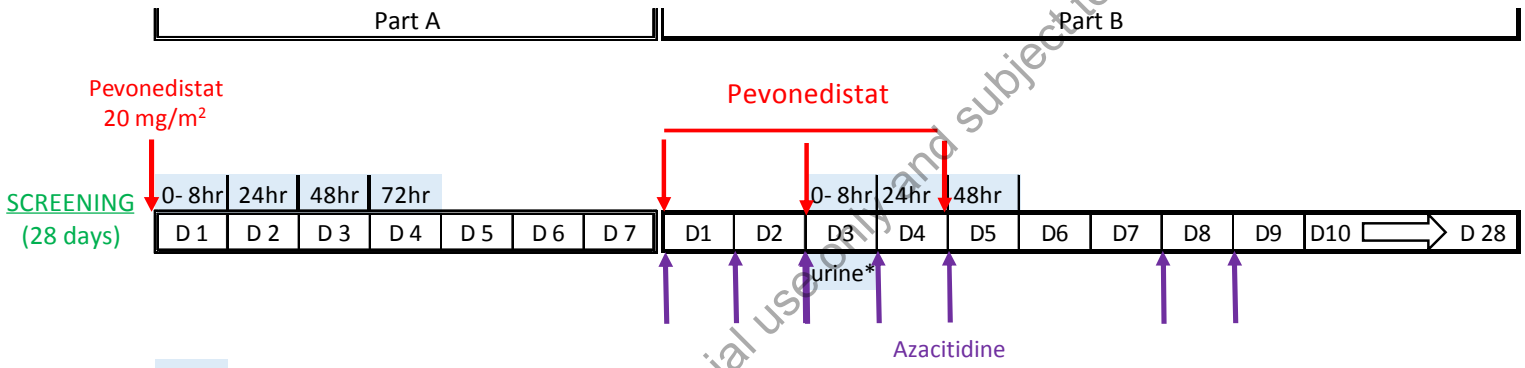
[b] The sample is to be collected at the end of pevonedistat infusion (immediately before stopping the IV infusion). The pevonedistat infusion takes approximately 1 hour.

[c] The time of sample collection is to be based on the time of completion of pevonedistat IV infusion on Day 3.

[d] The time of sample collection is to be based on the time of initiation of pevonedistat IV infusion on Day 3.

Appendix B Study Diagrams

PEVONEDISTAT-1016 PART A: SINGLE DOSE PEVONEDISTAT AND PART B: PEVONEDISTAT IN COMBINATION WITH AZACITIDINE (PATIENTS WITH HEMATOLOGIC MALIGNANCIES)



D, Day; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous

In Part A, patients will receive a single dose of pevonedistat for PK assessment. In Part B, patients with hematologic malignancies will receive an IV infusion of pevonedistat on Days 1, 3, and 5 in combination with azacitidine SC on Days 1–5, 8, and 9 in a 28-day treatment period. Part B may start 4-7 days after the dose of pevonedistat administered in Part A. Intrapatient dose escalation may start in Cycle 2 or in subsequent cycles. See Section 8.1 for details of study drug administration.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	23-Feb-2022 13:48 UTC