CLINICAL STUDY PROTOCOL

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

Protocol Version and Date:

Version 4.0: 01-June-2021

PROTOCOL

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

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

Sponsor: Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington, MA 02421

Study Number: Pevonedistat-1016

EudraCT Number: 2018-004049-17

Compound: Pevonedistat (TAK-924/MLN4924)

Date: 27 May 2021 **Version/Amendment Number:** 4

Amendment History:

Date	Amendment No.	Amendment Type	Region
27 May 2021	4	Substantial	Global
04 November 2020	3	Substantial	Global
29 June 2020	2	Substantial	Global
25 February 2019	1	Substantial	Global
07 November 2018	Initial protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

Takeda Development Center–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America	Europe
Serious adverse event and pregnancy reporting	See Section 10.0	See Section 10.0
Medical Monitor (medical advice on protocol and compound)	Refer to Study Manual	Refer to Study Manual
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Refer to Study Manual	Refer to Study Manual

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted] MD Date
(or designee)

[redacted] PhD Date
(or designee)

[redacted] PhD Date
(or designee)

[redacted] PhD Date
(or designee)

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix C).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment 4 Summary of Changes

Protocol Amendment 4 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reason for this amendment is to update the name of the legal entity to Takeda Development Center Americas, Inc. and to update its address. In addition, the text on the posttrial access (PTA) program and its duration are clarified, a clarification in the schedule of events is provided, and a corrected study diagram is provided.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Title page Section 2.0 STUDY SUMMARY Section 3.4 Corporate Identification	Updated the name and address of legal entity to Takeda Development Center Americas, Inc., 95 Hayden Avenue, Lexington, MA 02421	Update to name of the legal entity and its address.
2.	Section 6.3.5 PTA	Updated and clarified text on the posttrial access program and its duration.	Change made to include the current approach by the sponsor.
3.	Section 7.2 Exclusion Criteria Item 20.	Added multigated acquisition scan for the determination of left ventricular ejection fraction (LVEF) at screening.	Change made to increase flexibility of measurements.
4.	Appendix A SOE SOE for Part A: Single Agent Pevonedistat and PK (All Patients) Footnotes	Updated Schedule of Events (SOE) table to include (LVEF) screening timing.	Clarified timing of LVEF in the SOE previously included in the Exclusion Criteria.
5.	Appendix B Study Diagrams	Replaced Study Diagram for patients with hematologic malignancies	Correction of an error in the designation of study days in Part A of the Study Diagram (no change made to study conduct/assessments).

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	Compound: Pevonedistat (TAK-924; MLN4924)
Title of Protocol: 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	**EudraCT No.:** 2018-004049-17
Study Number: Pevonedistat-1016	**Phase:** 1/1b

Study Design:

This study is an open-label, multicenter, 2-part study. The study has been designed to characterize the pharmacokinetics (PK) of pevonedistat and assess the safety of pevonedistat in combination with select standard of care (SOC) agents in patients with myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), acute myelogenous leukemia (AML), or advanced solid tumors who also have severe renal impairment or mild/moderate hepatic impairment. Patients will be assigned to 1 of 4 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).

Part A of the study will be a single-agent PK assessment period with pevonedistat. All eligible patients will be administered a single dose of pevonedistat 20 mg/m^2 via an approximately 1-hour intravenous (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 an approximate 4- to 7-day washout period before the start of Part B.

In Part B, patients will receive pevonedistat in combination with SOC agents (azacitidine, docetaxel, or carboplatin plus paclitaxel).

Patients with hematologic malignancies (MDS, CMML, or AML) may receive pevonedistat on Days 1, 3, and 5 in combination with azacitidine (75 mg/m^2,) on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles. Patients will receive azacitidine subcutaneously (SC) in Cycle 1. Azacitidine will be given SC or IV during Cycle 2 and beyond. During Cycle 1 of Part B, plasma and urine PK samples for measurement of 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.

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 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 United States Prescribing Information/Summary of Product Characteristics recommendations.

Patients may continue to receive the combination treatment (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 toxicities. Patients may discontinue therapy at any time. Patients will attend the end of study (EOS) 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 performance status (ECOG PS) will be assessed, and electrocardiograms, 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, version 5.0, effective date 27 November 2017 [1]. Guidelines for dose modifications are provided as per the study protocol.

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

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.

Secondary Objectives:

The secondary objectives (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.

Safety Objective:

The safety objective (Part A and Part B) is 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.

Patient Population: Male or female patients aged 18 years or older with higher-risk (HR) MDS, HR CMML, AML, or advanced solid tumors, with various degrees of renal or hepatic function.

Number of Patients:	**Number of Sites:**
Approximately 42 patients will be enrolled in the study.	There will be approximately 25 to 30 sites in the United States and European Union.
Dose Level(s): **Part A** Single dose of pevonedistat 20 mg/m^2 via a 1-hour IV infusion. **Part B** After completion of Part A, all patients will be given an opportunity to continue treatment in Part B. Patients with hematologic malignancies may receive pevonedistat on Days 1, 3, and 5 in combination with azacitidine (75 mg/m^2) on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles. Patients will receive azacitidine SC in Cycle 1. Azacitidine will be given SC or IV during Cycle 2 and beyond. Starting doses: pevonedistat 20 mg/m^2 and azacitidine 75 mg/m^2 (Control Arm and Mild Hepatic Arm);	**Route of Administration:** Pevonedistat, docetaxel, carboplatin, and paclitaxel: IV Azacitidine: IV or SC

pevonedistat 10 mg/m^2 and azacitidine 75 mg/m^2 (Moderate Hepatic Arm); pevonedistat 15 mg/m^2 and azacitidine 75 mg/m^2 (Renal Arm). Based on available safety data, patients who tolerate treatment well at the initially assigned dose of pevonedistat may be allowed to increase their dose of pevonedistat in increments of 5 mg/m^2 per cycle. Maximum doses: pevonedistat 20 mg/m^2 and azacitidine 75 mg/m^2. 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. Only patients in the Renal Arm will receive treatment with pevonedistat in combination with docetaxel. Starting doses: pevonedistat 20 mg/m^2 and carboplatin area under the plasma concentration-time curve (AUC)4 plus paclitaxel 135 mg/m^2 (Mild Hepatic Arm); pevonedistat 10 mg/m^2 and carboplatin AUC4 plus paclitaxel 90 mg/m^2 (Moderate Hepatic Arm); pevonedistat 15 mg/m^2 and docetaxel 75 mg/m^2 or carboplatin AUC4 plus paclitaxel 135 mg/m^2 (Renal Arm). Maximum doses: pevonedistat 20 mg/m^2 and carboplatin AUC5 plus paclitaxel 135 mg/m^2(Mild Hepatic Arm); pevonedistat 20 mg/m^2 and carboplatin AUC5 plus paclitaxel 90 mg/m^2 (Moderate Hepatic Arm); pevonedistat 25 mg/m^2 and docetaxel 75 mg/m^2; pevonedistat 20 mg/m^2 and carboplatin AUC5 plus paclitaxel 175 mg/m^2 (Renal Arm).	
Duration of Treatment: **Part A:** Approximately 4 to 7 days, including the pevonedistat single-dose PK assessment and washout. **Part B:** The maximum duration of treatment with pevonedistat in combination with SOC agents (azacitidine, docetaxel, or carboplatin plus paclitaxel) is 12 cycles (28-day cycles for patients with hematologic malignancies and 21-day cycles for patients with advanced solid tumors), unless the investigator and sponsor (or designee) agree that a patient would benefit from continued treatment.	**Period of Evaluation:** Screening: Within 28 days before the first dose of study drug in Part A. **Part A:** Pevonedistat single-dose for PK assessment: Days 1 to 4. Washout: 4 to 7 days. **Part B:** Patients may continue to receive the combination 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. Follow-up: Patients will attend an EOS visit 30 days (+10 days) after the last dose of study drugs or before the start of subsequent alternative anticancer therapy, if that occurs sooner.

Main Criteria for Inclusion:

All Patients:

- Male and female patients aged 18 years or older.
- Expected survival of at least 3 months from the date of enrollment in the study.
- ECOG PS of 0, 1, or 2.
- Recovered (ie, Grade ≤1 toxicity) from the reversible effects of prior anticancer therapy.
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤1.5 × upper limit of the normal range (ULN) at screening or within 7 days before the first dose of study drug.
- Female patients who:
  - Are postmenopausal for at least 1 year before the screening visit, OR
  - Are surgically sterile, OR
  - Agree, if they are of childbearing potential, to practice 1 highly effective method of contraception and 1 additional effective (barrier) method, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, OR
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.
- Male patients, even if surgically sterilized (ie, status postvasectomy), who:
  - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.
- Suitable venous access for the study-required blood sampling (ie, PK sampling).
- Voluntary written consent must be given by the patient or the patient's legally acceptable representative before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient or the patient's legally acceptable representative at any time without prejudice to future medical care.

Patients with Hematologic Malignancies:

- Previously untreated hematologic malignancies not suitable for induction therapy.
- Morphologically confirmed diagnosis of MDS or nonproliferative CMML (ie, with white blood cells [WBC] <13,000/μL) at study entry, based on one of the following:

French-American-British Classifications [2]:

  - Refractory anemia with excess blasts (RAEB), defined as having 5% to 20% myeloblasts in the bone marrow.
  - CMML with 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood.

OR

World Health Organization (WHO) Classifications [3]:

  - RAEB-1, defined as having 5% to 9% myeloblasts in the bone marrow.
  - RAEB-2, defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood.
  - CMML-2, defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood.
  - CMML-1 (although CMML-1 is defined as having <10% myeloblasts in the bone marrow and/or <5% blasts in the blood, these patients may enroll only if bone marrow blasts ≥5%).

- All patients with MDS or CMML must also have one of the following Prognostic Risk Categories at study entry, based on the Revised International Prognostic Scoring System [4]:
  - Very high (>6 points).
  - High (>4.5-6 points).
  - Intermediate (>3-4.5 points): A patient determined to be in the Intermediate Prognostic Risk Category is only allowable in the setting of ≥5% bone marrow myeloblasts.
- Patients with WHO-defined AML at study entry, including leukemia secondary to prior chemotherapy or resulting from an antecedent hematologic disorder, who have failed to achieve CR or who have relapsed after prior therapy and are not candidates for potentially curative treatment.
- Patients with relapsed or refractory MDS at study entry, who have previously been treated with an hypomethylating agents.

For patients with hematologic malignancies, laboratory value requirements per study arms for estimated glomerular filtration rate (eGFR), total bilirubin, and alanine aminotransferase (ALT) are provided in the table, below:

Treatment Arm	eGFR (mL/min/1.73 m^2)	Total Bilirubin	ALT
Control	≥90	≤ULN	≤ULN
Renal	<30	≤ULN	≤2.5 × ULN
Mild Hepatic	≥60	ULN <bilirubin ≤1.5 × ULN (not secondary to transfusions)	Any
Moderate Hepatic	≥60	1.5 × ULN <bilirubin ≤3.0 × ULN (not secondary to transfusions)	Any

Patients with Advanced Solid Tumors:

- Adult patients who have a histologically or cytologically confirmed metastatic or locally advanced solid tumor that is appropriate for treatment with pevonedistat in combination with either docetaxel or carboplatin plus paclitaxel in Part B of this study, or have progressed despite standard therapy, or for whom conventional therapy is not considered effective.
- For patients with advanced solid tumors, clinical laboratory values as specified below:
  - Hemoglobin ≥8 g/dL. Patients may be transfused to achieve this value.
  - For patients to be treated with pevonedistat plus docetaxel in Part B, total bilirubin must be ≤ULN.
  - ALT, aspartate aminotransferase (AST), and alkaline phosphatase ≤2.5 × ULN.
    - For patients to be treated with pevonedistat plus docetaxel in Part B, AST and ALT must be ≤1.5 × ULN. Only patients with severe renal impairment may be considered for this combination.
  - Absolute neutrophil count ≥1,500/mm^3.
  - Platelet count ≥100,000/mm^3.
  - Albumin ≥2.7 g/dL.
- Computerized tomography scan or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis within 28 days of the first dose of study drug.

For patients with advanced solid tumors, laboratory value requirements per study arms for eGFR, total bilirubin, and ALT are provided in the table, below:

Treatment Arm	eGFR (mL/min/1.73 m^2)	Total Bilirubin	ALT
Renal	<30	≤ULN	≤1.5 × ULN (for pevonedistat plus docetaxel) ≤2.5 × ULN (for pevonedistat plus carboplatin plus paclitaxel)
Mild hepatic	≥60	ULN <bilirubin ≤1.5 × ULN	Any
Moderate hepatic	≥60	1.5 × ULN <bilirubin ≤3.0 × ULN	Any

Main Criteria for Exclusion:

All Patients:

- Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures or could limit expected patient survival to less than 6 months.
- End-stage renal disease requiring hemodialysis at study entry.
- Gilbert syndrome.
- Treatment with any investigational products or participation in any interventional studies within 21 days before the first dose of any study drug.
- Known hypersensitivity to pevonedistat or its excipients.
- Active uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, or septicemia. Prophylactic treatment with antibiotics is allowed.
- Major surgery within 14 days before first dose or a scheduled surgery during study period; insertion of a venous access device (eg, catheter, port) is not considered major surgery.
- Life-threatening illness unrelated to cancer.
- Known HIV seropositive.
- Known hepatitis B surface antigen seropositive, or known or suspected active hepatitis C infection.
- Known hepatic cirrhosis or severe pre-existing hepatic impairment.
- Known cardiopulmonary disease defined as unstable angina, clinically significant arrhythmia, congestive heart failure (New York Heart Association Class III or IV), and/or myocardial infarction within 6 months before first dose.
- Prolonged rate corrected QT interval ≥500 msec, calculated according to institutional guidelines.
- Treatment with strong cytochrome P450 (CYP3A) inducers within 14 days before the first dose of pevonedistat.
- Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 of Part A, before first dose of study drug.
- Female patients who intend to donate eggs (ova) during the course of this study or for 6 months after receiving their last dose of study drug(s).
- Male patients who intend to donate sperm or father a child during the course of this study or for 4 months after receiving their last dose of study drug(s).
- Diagnosed or treated for a different malignancy within 2 years before randomization or previously diagnosed with a different malignancy with any current evidence of residual disease.
- High blood pressure that cannot be controlled by standard treatments.
- Left ventricular ejection fraction <50% within 6 months prior to study enrollment.
- Severe uncontrolled ventricular arrhythmias or torsade de pointes; electrocardiographic evidence of acute ischemia or active conduction system abnormalities; or clinically significant arrhythmia.
- Severe symptomatic pulmonary hypertension requiring pharmacologic therapy or patients with chronic respiratory disease that require continuous oxygen.

Patients with Hematologic Malignancies:

- Acute promyelocytic leukemia as diagnosed by morphologic examination of bone marrow, by fluorescent in situ hybridization or cytogenetics of peripheral blood or bone marrow, or by other accepted analysis.

- Patients with AML with a WBC count ≥50,000/μL. Patients who are cytoreduced with leukapheresis or with hydroxyurea may be enrolled if they otherwise meet the eligibility criteria.
- Patients with either clinical evidence of or history of central nervous system (CNS) involvement by AML.
- Known hypersensitivity to azacitidine or its excipients.
- For patients with hematologic malignancies, PT or aPTT >1.5 × ULN or active uncontrolled coagulopathy or bleeding disorder. Patients therapeutically anticoagulated with warfarin, direct thrombin inhibitors, direct factor Xa inhibitors, or heparin are excluded from enrollment.

Patients with Advanced Solid Tumors:

- Prior treatment with radiation therapy involving ≥25% of the hematopoietically active bone marrow.
- Known hypersensitivity or history of severe intolerance or toxicity to chemotherapeutic agents, including known history of severe hypersensitivity reactions to docetaxel (polysorbate 80-based formulations) for patients to be treated with pevonedistat in combination with docetaxel; history of hypersensitivity to carboplatin for patients to be treated with pevonedistat plus carboplatin plus paclitaxel; or history of severe hypersensitivity to paclitaxel (Cremophor-based formulations) for patients to be treated with pevonedistat with carboplatin plus paclitaxel.
- CNS metastasis, except for patients who have received prior treatment (radiation or resection) and have stable CNS disease (eg, stable MRI, no steroid requirement).

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

- 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.

Secondary Endpoints:

- Terminal disposition phase half-life ($t_{1/2z}$) of pevonedistat following single- and multiple-dose administration.
- C_{max} of pevonedistat following multiple-dose administration.
- Fraction of unbound drug in plasma (f_u) of pevonedistat.
- C_{max} of azacitidine following multiple-dose administration.
- Time of first occurrence of maximum observed concentration 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 of pevonedistat and azacitidine following multiple-dose administration.
- Clearance of pevonedistat and apparent clearance of azacitidine.
- Renal clearance of pevonedistat and azacitidine.
- Volume of distribution at steady-state (V_{ss}) of pevonedistat and apparent V_{ss} of azacitidine.
- Measures of disease response (CR, complete remission with incomplete blood count recovery [CRi] or PR for AML; CR, PR, or HI for MDS and CMML; CR or PR for solid tumors using the Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1 criteria); including response rate and duration of response, based on the investigator's assessment (Part B only).

Safety Endpoints:

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

Statistical Considerations:

Analyses will be primarily descriptive in nature. No formal statistical hypothesis testing will be performed. A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

Summary tabulations will be presented to display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables along with the number and percentage (calculated using nonmissing values) per category for categorical data, unless specified otherwise.

PK: 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 organ function group. 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 organ function group and by dose levels. Plasma pevonedistat and/or azacitidine PK parameters for each patient will be calculated using noncompartmental analysis methods.

The analysis for the effects of organ impairment on pevonedistat PK will be based on unbound pevonedistat plasma exposure (AUC) following a single dose of pevonedistat in Part A. To assess the effects of severe renal impairment or mild or moderate 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), mild hepatic impairment (Mild Hepatic Arm) versus the normal group (Control Arm), and moderate hepatic impairment (Moderate Hepatic Arm) versus the normal group (Control Arm). The ANOVA results will be used to estimate the ratios of LS geometric means (severe renal impairment vs normal, and mild or moderate hepatic impairment vs normal) and corresponding 90% CIs for pevonedistat unbound AUC. The PK-evaluable population will be used for these analyses.

Efficacy: Efficacy measures will include disease response and duration of disease response. Analysis of all efficacy measures will be descriptive. Disease response in AML will be based on the overall response rate (CR + 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]. For AML patients, all CR includes both CR and CRi. Disease response in patients with MDS or CMML will be based on the best overall response (CR + PR + HI) as determined by the investigator using the revised IWG response criteria for MDS [6].

Disease response to pevonedistat in combination with docetaxel or carboplatin plus paclitaxel will be based on the best overall response as determined by the investigator using RECIST version 1.1 guidelines.

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 PD or death if no prior PD is documented. Responders without disease progression will be censored at the last clinical assessment of response.

Safety:

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 on the basis of the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory values using the safety population. Exposure to the study drugs and reasons for discontinuation will be tabulated.

Sample Size Justification: The sample size calculation is based on the number of patients required to adequately characterize the PK of pevonedistat in the organ impairment arms (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 Arm (normal renal and hepatic function) and 9 to 12 patients in each of the 3 organ impairment arms. Patients who are considered nonevaluable may be replaced. The sample size of approximately 9 patients specified as being required for the PK-evaluable 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 percent coefficient of variation in pevonedistat AUC_{∞} of 43.8% (Study C15011).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
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 from time zero to the end of the dosing interval
BCRP	breast cancer resistance protein
BDC	bile in bile duct–cannulated
BSA	body surface area
CDLs	cullin-dependent ubiquitin E3 ligases
CL	total clearance
CL/F	apparent clearance
CL_R	renal clearance
CMML	chronic myelomonocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response/remission
CRi	complete remission with incomplete blood count recovery
CrCL	creatinine clearance
CRO	contract research organization
CSR	clinical study report
CT	computerized tomography
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study

ET	early termination
EU	European Union
FDA	[United States] Food and Drug Administration
f_u	fraction of unbound drug in plasma
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
HI	hematologic improvement
HR CMML	higher-risk chronic myelomonocytic leukemia
HR MDS	higher-risk myelodysplastic syndromes
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MDS	myelodysplastic syndromes
MHRA	Medicines and Healthcare products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEDD8	neural precursor cell expressed, developmentally down-regulated 8
ORR	overall response rate
PBPK	physiologically based pharmacokinetic(s)
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response/remission
PS	performance status
PT	prothrombin time
PTA	posttrial access
PTE	pretreatment event

RAEB	refractory anemia with excess blasts
RBC	red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SOC	standard of care
SOE	schedule of events
SC	subcutaneous(ly)
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
T_{max}	time of first occurrence of maximum observed concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia
USPI	US Prescribing Information
V_{ss}	volume of distribution at steady-state
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.

4.0 INTRODUCTION

4.1 Background

As of 22 January 2020, an estimated 794 patients received active treatment with pevonedistat, either as a single agent or in combination with other therapeutic agents in hematologic malignancies (N = 508) or in solid tumors (N = 286).

Pevonedistat is currently in phase 2/3 of clinical development for higher-risk myelodysplastic syndromes (HR MDS), HR chronic myelomonocytic leukemia (HR CMML), and low-blast acute myelogenous leukemia (AML). The recommended phase 2 dose (RP2D) of pevonedistat administered as a single agent in patients with advanced hematologic malignancy is 50 mg/m^2 on Days 1, 3, and 5 in 21-day cycles.

Pevonedistat is currently under development as a component of regimens with azacitidine. Two clinical studies with pevonedistat and azacitidine are ongoing as of 22 January 2020; Pevonedistat-2001 (P2001), a phase 2 study, and Pevonedistat-3001 (P3001), a phase 3 study, are both in patients with HR MDS, HR CMML, or low-blast AML. Preliminary data from interim analysis 2 of Study P2001 suggest potential clinical benefit in terms of longer overall survival and event-free survival among patients with HR MDS/CMML or low-blast AML receiving the combination treatment of pevonedistat plus azacitidine versus azacitidine alone.

Pevonedistat is also being evaluated in combination therapy with standard of care (SOC) agents (eg, pevonedistat plus docetaxel or pevonedistat plus carboplatin/paclitaxel) for patients with solid tumors. Additive/synergistic effects of docetaxel and carboplatin/ paclitaxel in combination with pevonedistat have been studied in a number of in vitro and in vivo models by the sponsor [7,8]. In patients with solid tumors, the maximum tolerated dose (MTD) and RP2D of pevonedistat in combination with docetaxel is 25 mg/m^2 pevonedistat dosed on Days 1, 3, and 5, and 75 mg/m^2 docetaxel on Day 1 in 21-day cycles. The MTD and RP2D of pevonedistat in combination with carboplatin/paclitaxel is 20 mg/m^2 pevonedistat dosed on Days 1, 3, and 5 and 175 mg/m^2 paclitaxel plus area under the plasma concentration-time curve (AUC)5 carboplatin on Day 1 in 21-day cycles.

4.1.1 Study Drug

Pevonedistat is a first-in-class, small molecule inhibitor of neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)-activating enzyme (NAE) under development for the treatment of malignancies. NAE, an E1 activating enzyme, is an essential component of the NEDD8 conjugation pathway, which controls the activity of cullin-dependent ubiquitin E3 ligases (CDLs). Once activated, CDLs are able to transfer ubiquitin to specific protein substrates, which targets them for proteasomal degradation. CDLs thereby control the timely ubiquitination and degradation of many proteins with important roles in cell cycle progression and signal transduction. Inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers, by preventing neddylation and activation of the CDLs, thus disrupting proteasomal degradation of a variety of critical regulatory proteins integral to tumor cell growth, proliferation, and survival.

4.1.2 Nonclinical Background

Pevonedistat is a potent and selective inhibitor of NAE activity. Pevonedistat also inhibits human carbonic anhydrase II, which may explain the extensive partitioning of pevonedistat in red blood cells (RBCs) that has been observed in animal species and humans.

Pevonedistat showed medium permeability in Caco-2 cells.

Plasma clearance ranged from relatively low in chimpanzees, to moderate in dogs and monkeys, to relatively high in rats. The plasma terminal disposition phase half-life ($t_{1/2z}$), calculated as $\ln(2)\lambda_z$ varied from <1 hour in rats to approximately 15 hours in monkeys.

The major elimination pathway of pevonedistat in animals is through the hepatic route. Urinary excretion of unchanged pevonedistat was negligible in rats, monkeys, and chimpanzees. After an intravenous (IV) dose of [^{14}C]pevonedistat, radioactivity was primarily excreted in the feces in intact rats and in bile in bile duct–cannulated (BDC) rats; excretion was almost complete by 24 hours postdose. Similar to results in intact rats, IV infusion of [^{14}C]pevonedistat to intact beagle dogs resulted in most of the administered dose being eliminated in the feces. In BDC beagle dogs, however, most of the dose was eliminated in the urine and bile. In both intact and BDC beagles, most of the radioactivity in the excreta was recovered over 24 hours after the start of infusion.

Detailed information regarding the nonclinical pharmacology and toxicology of pevonedistat may be found in the current investigator's brochure (IB).

4.1.3 Clinical Background Information

4.1.3.1 Clinical Pharmacokinetics

Population pharmacokinetic (PK) analysis was conducted using data from pevonedistat single-agent studies (Studies C15001, C15002, C15003, and C15005) and pevonedistat in combination with SOC chemotherapy (Studies C15009, C15010, Pevonedistat-1012 [P1012], and P2001) in patients with solid tumor or hematologic malignancies. As of 22 January 2020, the database contained 416 evaluable patients contributing 4689 PK observations. Pevonedistat plasma concentration-time profiles were well described by a 2-compartment model with linear elimination. Coadministration with azacitidine or docetaxel did not appear to affect the total clearance (CL) of pevonedistat, whereas concurrent administration of carboplatin and paclitaxel decreased the CL of pevonedistat by approximately 50%, translating to an approximately 100% higher pevonedistat exposure (AUC) during coadministration with carboplatin and paclitaxel, consistent with pevonedistat concentration data observed in Study C15010. Race, sex, age, tumor type (hematologic vs solid), mild or moderate renal impairment (creatinine clearance [CrCL] ≥30 mL/min), and mildly impaired liver function, to the extent represented in this dataset (ie, total bilirubin ≤upper limit of the normal range [ULN] and alanine aminotransferase [ALT]/aspartate aminotransferase [AST] ≤2.5 × ULN), had no impact on pevonedistat PK.

An open-label drug-drug interaction (DDI) Study C15011 evaluated the cytochrome P450 (CYP)3A-mediated inhibitory effects of fluconazole and itraconazole on pevonedistat PK in patients with advanced solid tumors. The results indicated that itraconazole, a strong CYP3A/

P-glycoprotein (P-gp) inhibitor, and fluconazole, a moderate CYP3A inhibitor, had no clinically meaningful effects on pevonedistat PK.

Study Pevonedistat-1015 (P1015) indicated that rifampin, a strong CYP3A inducer, had no clinically meaningful impact on pevonedistat systemic exposures. Despite results of Studies C15011 and P1015, in the current study, use of strong CYP3A inducers and inhibitors remains prohibited in order to interpret the effects of organ impairment on pevonedistat PK without other confounding factors.

Study P1012 is a phase 1/1b, open-label study of pevonedistat as single agent and in combination with azacitidine in adult East Asian patients with AML or MDS enrolled in Japan, South Korea, and Taiwan. Pevonedistat 20 mg/m^2 in combination with 75 mg/m^2 azacitidine was determined to be the MTD/RP2D in Asian patients. The analysis indicated that the systemic exposure of pevonedistat was similar among major East Asian races, ie, Japanese, Korean, and Chinese. Furthermore, the systemic exposures of pevonedistat was comparable between East Asian and Western patients. These results support the same RP2/3D of pevonedistat in combination with azacitidine in global patient population.

4.1.3.2 Clinical Experience

As of 22 January 2020, an estimated 794 patients received active treatment with pevonedistat, including 508 patients with hematologic indications and 286 patients with solid tumor indications. These include 227 patients diagnosed with advanced malignancies, including solid tumors, AML, melanoma, lymphoma, multiple myeloma, HR MDS, and acute lymphoblastic leukemia, who participated in studies of single-agent pevonedistat.

In completed combination studies in patients with hematologic malignancies, 64 elderly patients with treatment-naïve AML (Study C15009) were treated with pevonedistat plus azacitidine [9]; and 23 East Asian patients with World Health Organization (WHO)-defined AML or HR MDS have received a single IV dose of pevonedistat alone and in combination with azacitidine (Study P1012).

In completed combination studies in patients with solid tumors, 64 patients have received combination treatments with docetaxel, gemcitabine, or a combination of carboplatin and paclitaxel (Study C15010); and 51 patients have received a single IV dose of pevonedistat alone and in combination with the CYP3A inhibitor probes itraconazole or fluconazole (36 of these 51 patients then continued receiving pevonedistat plus SOC, either docetaxel, or carboplatin plus paclitaxel) (Study C15011).

Eight patients with advanced solid tumors have received a single dose of [^{14}C]-pevonedistat (7 of these 8 patients then continued receiving pevonedistat plus SOC, either docetaxel, or carboplatin plus paclitaxel) (Study Pevonedistat-1013 [P1013]).

In ongoing combination studies, 58 patients with HR MDS, CMML, or low-blast AML have received combination treatment with azacitidine and pevonedistat (Study P2001), and it is estimated that 222 patients with HR MDS, CMML, or low-blast AML have received combination treatment with azacitidine and pevonedistat in Study P3001.

Pevonedistat has reported single-agent clinical activity in a phase 1 study (Study C15003) in patients with relapsed/refractory AML. In Study C15003, a total of 66 patients with AML were treated in a variety of patient settings, including after relapse following allogeneic transplant as well as with therapy-related AML, and primary refractory AML. In the phase 1 trial, 7 responses (2 complete remissions [CR] and 5 partial remissions [PR]) were observed among 55 response-evaluable patients with AML who received pevonedistat monotherapy. Investigators should note that some patients may benefit from continued treatment even though their bone marrow blast counts may fluctuate over the course of the first 4 cycles. For example, 2 of the 7 responders to pevonedistat given as a single agent in Study C15003 had asymptomatic, transient increases in bone marrow blasts after achieving a response. In these 2 cases, bone marrow blasts increased from less than 5% to more than 20%, and then went down. In addition, another responder in that study had an asymptomatic, transient increase in bone marrow blasts before achieving a response. In that case, bone marrow blasts almost doubled before response. These 3 patients were allowed to remain on study because their investigators felt they were clinically benefiting from continued treatment despite changes in their bone marrow blast counts.

Pevonedistat has clinical activity when administered in combination with azacitidine. Study C15009 evaluated the combination of escalating doses of pevonedistat plus azacitidine in 64 treatment-naïve patients with AML. The MTD was determined to be 20 mg/m^2 pevonedistat in combination with 75 mg/m^2 azacitidine. A total of 61 patients were treated at the MTD. Overall response rate (ORR) in the 64-patient intent-to-treat (ITT) cohort was 50% (20 CR, 5 complete remission with incomplete blood count recovery [CRi], 7 PR); median duration of remission was 8.3 months. Pevonedistat PK was not altered by the addition of azacitidine. The nature and frequency of the reported toxicities (excluding dose-limiting toxicities [DLTs]) were similar to previous reports for azacitidine alone [9]. Additional efficacy and safety information from Study C15009 is provided in Section 4.1.4.2.

Pevonedistat has clinical activity when administered in combination therapy with docetaxel or carboplatin plus paclitaxel. In Study C15010, the ORR for patients treated with pevonedistat in combination with docetaxel was 16% (3 PRs in a response-evaluable population of 19 patients) [7]. For patients treated with pevonedistat in combination with carboplatin plus paclitaxel the ORR (CR + PR) was 35% (2 CRs and 6 PRs in a response-evaluable population of 23 patients). In Study C15011, the ORR (CR + PR) among 28 patients who received treatment with pevonedistat in combination with chemotherapy was 14.3% (10.5% in the pevonedistat plus docetaxel arm and 22.2% in the pevonedistat plus carboplatin plus paclitaxel arm; 2 patients in each arm). A total of 4 patients (14.3%) achieved PR and 16 patients (57.1%) had stable disease (SD); 8 patients (28.6%) had a best response of progressive disease (PD). Ongoing studies that include patients with solid tumors (Studies Pevonedistat-1014 and P1015) have not resulted in any new safety signals for the combination of pevonedistat with docetaxel or carboplatin plus paclitaxel.

Refer to the IB, which will be updated regularly throughout the duration of this study, for further details on the clinical development program for pevonedistat.

4.1.4 Potential Risks and Benefits

4.1.4.1 Azacitidine

In clinical studies, adverse reactions to azacitidine were qualitatively similar between the IV and subcutaneous (SC) routes of administration [10]. In clinical studies with SC administration of azacitidine, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of azacitidine. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of SC treatment compared with later cycles, and included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia. There did not appear to be any adverse reactions that increased in frequency over the course of treatment.

Adverse reactions that appeared to be specifically associated with the IV route of administration included infusion site reactions (eg, erythema or pain) and catheter site reactions (eg, infection, erythema, or hemorrhage).

Adverse reactions identified during postmarketing use of azacitidine include interstitial lung disease, tumor lysis syndrome, injection site necrosis, Sweet's syndrome (acute febrile neutrophilic dermatosis), and necrotizing fasciitis (including fatal cases).

Refer to the VIDAZA (azacitidine) United States Prescribing Information (USPI) [10], or the European Union (EU) Summary of Product Characteristics (SmPC) [11], as applicable, for the most recent information regarding the anticipated risks and benefits of azacitidine.

4.1.4.1.1 Anemia, Neutropenia, and Thrombocytopenia

Azacitidine causes anemia, neutropenia, and thrombocytopenia. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, before each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response (see Section 8.3).

4.1.4.1.2 Severe Pre-existing Hepatic Impairment

Caution is needed in patients with liver disease when administering azacitidine. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L [12]. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

4.1.4.1.3 Renal Abnormalities

Patients with renal impairment should be closely monitored for toxicity because azacitidine and its metabolites are primarily excreted by the kidneys. Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with IV azacitidine in combination with other chemotherapeutic agents for non-MDS conditions. Renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an

alkaline urine and hypokalemia (serum potassium <3 mEq/L), developed in 5 patients with CMML treated with azacitidine and etoposide.

4.1.4.2 Pevonedistat Plus Azacitidine

Study C15009 was a phase 1b study that evaluated the MTD of pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28-day treatment cycle in patients aged 60 years or older with treatment-naïve AML who were unlikely to benefit from standard induction therapy. A total of 64 patients were treated (ITT population) at 2 dose levels. Pevonedistat dosing started at 20 mg/m^2 (n = 6) and increased to 30 mg/m^2 (n = 3) in the absence of DLTs. During dose escalation, at the 30 mg/m^2 dose level, 2 of the 3 patients experienced a DLT: 1 patient had persistent Grade 2 bilirubin elevation, and 1 patient had reversible Grade 4 AST elevation. Transaminase and bilirubin elevations were transient and clinically inconsequential in both patients (resolving to Grade 1 or baseline levels within 1 week after withdrawal from study). The MTD was determined to be 20 mg/m^2 pevonedistat in combination with 75 mg/m^2 azacitidine. An additional 55 patients were treated at the MTD, for a total of 61 patients treated at the MTD.

Patients in the ITT cohort (n = 64) received a median of 4 cycles (range, 1-37), and 23 of 64 patients (36%) received ≥6 cycles of pevonedistat plus azacitidine. The most common adverse events (AEs) were constipation (48%), nausea (42%), fatigue (42%), and anemia (39%). Fifty-three patients (82%) experienced Grade ≥3 AEs; the most frequent (≥15%) were anemia, febrile neutropenia (each 30%), thrombocytopenia (23%), neutropenia (20%), and pneumonia (17%). AST/ALT elevations Grade ≥3 were reported in 6% of patients. Forty-four patients (69%) experienced serious adverse events (SAEs); the most frequent (≥10%) were febrile neutropenia (25%) and pneumonia (14%). In addition to the 2 patients who withdrew because of DLTs, 2 patients withdrew from the study because of therapy-related toxicity (febrile neutropenia). In the MTD expansion cohort (n = 55), 2 additional patients experienced DLTs (Grade ≥3 transaminase elevation) and were successfully rechallenged with a reduced dose of pevonedistat. Both patients remained on study without further hepatic toxicity. There were 11 on-study deaths unrelated to study therapy. Pevonedistat PK was not altered by the addition of azacitidine.

The most detailed information on risks is provided in the IB and the Developmental Core Safety Information located within the IB.

Overall identified risks of pevonedistat include increased heart rate, diarrhea, nausea, vomiting, abnormal liver function tests, pyrexia, myalgia, and musculoskeletal pain.

Hepatotoxicity: Hepatotoxicity has been noted following administration of pevonedistat in patients with advanced malignancy, including elevations of liver transaminases (up to Grade 4), alkaline phosphatase (ALP; up to Grade 3), and bilirubin (up to Grade 3). Grade 1 through Grade 4 increases in ALT and AST have been observed in patients receiving single-agent pevonedistat for relapsed and/or refractory AML. The patients experiencing these changes in laboratory values have been asymptomatic. This type of elevation in transaminases had been observed previously in patients treated with pevonedistat. The elevations in laboratory values have been reversible with

dose modification including dose delay and reduction. Patients with elevated transaminases have been successfully rechallenged at lower doses.

Some events are considered potential risks of pevonedistat because of the occurrence of these events in phase 1 clinical studies in which single-agent pevonedistat was administered at doses substantially higher than those being used in current clinical trials. Those events included multiorgan failure that could result in death, renal failure, myelosuppression with increased susceptibility to infection, bleeding, anemia, acute phase response, gastrointestinal toxicity including or resulting in dehydration, electrolyte imbalance, and hypophosphatemia. Reported instances of cardiac arrhythmias were all supraventricular in origin, and all except 1 were deemed unrelated: the case of atrial fibrillation assessed by the investigator as related occurred in a patient with cardiovascular risk factors.

Other events, such as fatigue, chills, decreased appetite, febrile neutropenia, and gastrointestinal bleeding (all events assessed by an investigator as unrelated, the majority occurring in the setting of thrombocytopenia), are considered potential risks that are confounded by underlying disease or malignancy.

Potential risks that are derived from findings in animal studies in rats and dogs include myocardial degeneration and thrombosis; cardiovascular changes that could result in tachycardia; decreased or increased systolic blood pressure; increased diastolic blood pressure; pulmonary hypertension; enteropathy (including dehydration and electrolyte loss) with secondary sepsis; effects on testes and ovaries that represent a reproductive hazard, including sterility and increased developmental risk to fetus or embryo. Decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, high); this finding was considered adverse in the high-dose group, but no bone fractures were noted at any of the doses. Prolongation of the activated partial thromboplastin time (aPTT) and potential risk for local tissue injury are also associated with pevonedistat SC administration. Additional details may be found in the current IB.

Based on the known individual safety profiles of pevonedistat and azacitidine, the following potential risks of combination therapy may apply: myelosuppression, gastrointestinal events, electrolyte imbalances, hypophosphatemia, decreased renal function, hepatotoxicity, cardiac arrhythmias, cardiomyopathies, musculoskeletal pain, bleeding, and injection site reactions.

In Study C15009, patients received azacitidine as either an IV infusion or SC injection. Data from Study C15009 indicate that the route of azacitidine administration has no apparent effect on the safety profile of pevonedistat plus azacitidine.

4.1.4.3 Docetaxel

Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with non–small cell lung cancer who received prior platinum-based therapy receiving docetaxel at 100 mg/m^2.

Severe hypersensitivity, including very rare, fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of docetaxel and administration of appropriate therapy.

Docetaxel is contraindicated if the patient has a history of severe hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80.

Severe fluid retention may occur despite dexamethasone premedication.

For more details, refer to the docetaxel SmPC [13] or USPI [1].

4.1.4.3.1 Hepatotoxicity Warning

Docetaxel should not be given if total bilirubin is >ULN or if AST or ALT is ≥1.5 × ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with ALP are at increased risk for the development of Grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase >1.5 × ULN also had a higher rate of Grade 4 febrile neutropenia but did not have an increased incidence of toxic death. For this reason, patients with mild or moderate hepatic impairment will not be enrolled in the Part B arm incorporating docetaxel. Bilirubin, AST or ALT, and ALP values should be obtained prior to each cycle of docetaxel therapy and reviewed by the investigator.

4.1.4.3.2 Hematologic Warning

Docetaxel should not be given if the absolute neutrophil count (ANC) is less than 1500 cells/mm^3.

4.1.4.4 Pevonedistat Plus Docetaxel

The following potential risks, based on the known individual safety profiles of pevonedistat plus docetaxel, of combination therapy may apply: death, hypersensitivity, hepatotoxicity, neutropenia, and fluid retention (cardiac/pulmonary).

4.1.4.5 Carboplatin

Anaphylaxis-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

Vomiting is another frequent drug–related side effect.

Carboplatin injection is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds.

Carboplatin injection should not be employed in patients with severe bone marrow depression or significant bleeding.

For more details, refer to the carboplatin USPI [14] or SmPC [15].

4.1.4.5.1 Nephrotoxicity Warning

The major route of elimination for carboplatin is renal excretion. Renal effects of nephrotoxic compounds [16] (see Appendix K) may be potentiated by carboplatin. For patients with impaired renal function, carboplatin is given at 200 mg/m^2 or at a dose determined using the Calvert formula based on the glomerular filtration rate (GFR) of the patient. Treatment with carboplatin for patients with hepatic or renal impairment is administered at no higher than AUC5 based on safety profile of pevonedistat plus carboplatin plus paclitaxel in Study C15010.

4.1.4.5.2 Hematologic Warning

Bone marrow suppression is dose related and may be severe, resulting in infection or bleeding. Peripheral blood counts should be frequently monitored during carboplatin treatment and, when appropriate, until recovery is achieved.

Anemia may be cumulative and may require transfusion support.

4.1.4.6 Paclitaxel

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment; angioedema; and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical studies. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Severe conduction abnormalities have been documented in less than 1% of patients during paclitaxel therapy and, in some cases, require pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered, and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Paclitaxel is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor EL (polyoxyethylated castor oil).

For more details, refer to the paclitaxel USPI [16] or SmPC [17].

Paclitaxel injection therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3. To monitor for the occurrence of bone marrow suppression and primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel injection.

There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 × ULN. For patients with total bilirubin levels of 1.26 to 2 × ULN, paclitaxel should be given at 135 mg/m^2 over a 3-hour infusion period.

The effect of renal dysfunction on the disposition of paclitaxel has not been investigated.

4.1.4.7 Pevonedistat and Carboplatin Plus Paclitaxel

The following potential risks of combination therapy with pevonedistat and carboplatin plus paclitaxel may apply: bone marrow suppression, hypersensitivity/anaphylaxis reactions, and hepatotoxicity. A summary of hematologic toxicity of carboplatin alone and in combination with paclitaxel is provided in Appendix L.

4.1.5 Potential for DDIs

No formal clinical assessments of DDIs between azacitidine and other agents have been conducted. Please consult the VIDAZA USPI (Clinical Pharmacology [Section 12.3], Drug-Drug Interactions) for additional information [10]. Urinary excretion is the primary route of elimination of azacitidine and its metabolites. Pevonedistat is not a strong inhibitor or inducer for major CYP enzymes and drug transporters. The concomitant administration of pevonedistat is not expected to have clinically meaningful impact on azacitidine PK.

Pevonedistat concentration-time data were obtained from 64 treatment-naïve patients with AML who were administered pevonedistat in combination with azacitidine in Study C15009. Pevonedistat systemic exposures were not altered in the presence of azacitidine when compared with historical pevonedistat single-agent data (Study C15003), indicating that coadministration of azacitidine has no effects on pevonedistat PK.

Concurrent administration of carboplatin and paclitaxel decreased the CL of pevonedistat by approximately 50%, translating to an approximately 100% higher pevonedistat exposure (AUC).

The potential risk of DDIs between pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data (see IB). Study C15011 assessed the effect of multiple doses of fluconazole (a moderate CYP3A inhibitor) as well as the effect of multiple doses of itraconazole (a strong CYP3A/P-gp inhibitor) on pevonedistat PK. The result indicated that fluconazole or itraconazole has no clinically meaningful impact on pevonedistat PK. In Study P1015, co-administration of rifampin, a strong CYP3A inducer, with pevonedistat did not result in clinically meaningful alteration of pevonedistat systemic exposures [18]. Despite results of Studies C15011 and P1015, in the current study, use of strong CYP3A inducers and inhibitors remains prohibited in order to interpret the effects of organ impairment on pevonedistat PK without other confounding factors. As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored as the DDI potential between pevonedistat and other drugs has not been formally studied in humans. Patients should also be instructed to consult with the investigator before taking any new medications, including over-the-counter products and herbal supplements.

See Section 8.4 for information on concomitant medications that are prohibited and Section 8.5 for information on medications that are permitted during this study.

4.1.6 Summary of Risks and Benefits

Analyses of safety data from more than 130 patients treated with pevonedistat plus azacitidine at the dose and schedule to be used in this phase 1/1b study demonstrate that pevonedistat adds little

toxicity to azacitidine alone and that toxicities are manageable. Efficacy data from a phase 1 study using this combination demonstrated a 50% ORR based on an ITT analysis (20 CR, 5 CRi, 7 PR), with an 8.3-month median duration of remission in untreated, older patients with AML for whom intensive induction chemotherapy was considered inappropriate. In patients receiving ≥6 cycles of therapy (n = 23, 44%), ORR was 83%. In total, 6 out of 8 patients with a TP53 mutation achieved CR/CRi/PR, and 4 of 6 remained on study for >10 cycles. Baseline bone marrow blast percentage or cytogenetic/molecular risk did not influence ORR [9]. Thus, the benefit-risk ratio supports further study of the combination of pevonedistat and azacitidine in a randomized controlled trial in patients with HR MDS or CMML, or AML.

A number of patients with solid tumors treated with pevonedistat as a single agent demonstrated clinical benefit based primarily on prolonged SD. In addition, pevonedistat has clinical activity when administered in combination therapy with docetaxel or carboplatin plus paclitaxel. On the basis of findings from Study C15010 and Study C15011, these combinations have shown evidence of clinical benefit in the form of multiple PRs, limited CRs, and extended durations of SD. Therefore, it is considered that docetaxel and carboplatin plus paclitaxel may serve as reasonable partners in combination with pevonedistat for investigations in patients with various advanced solid tumors in this study.

4.2 Rationale for the Proposed Study

Pevonedistat is being developed in combination with azacitidine for the treatment of HR MDS, HR CMML, and AML and in combination with docetaxel or carboplatin plus paclitaxel for treatment of advanced solid tumors. Based on the preliminary results from the clinical radiolabeled mass balance study (Study P1013), pevonedistat undergoes extensive biotransformation with 41% and 53% of administered radioactivity recovered in urine and feces, respectively. Oxidative biotransformation pathways represented the major clearance mechanisms for pevonedistat, as inferred from metabolite profiling studies of excreta.

A population PK analysis of pevonedistat has been conducted with a wide range of renal function represented in the analysis population of cancer patients (CrCL, 26.3-301 mL/min; estimated glomerular filtration rate [eGFR] 24-267 mL/min/1.73 m^2). The analysis dataset included patients with renal impairment ranging from mild (N = 114 with CrCL of 60-89 mL/min; N = 157 with eGFR of 60-89 mL/min/1.73 m^2) or moderate (N = 57 with CrCL of 30-59 mL/min; N = 75 with eGFR of 30-59 mL/min/1.73 m^2). Renal function was not identified as a covariate in the population PK model, and it was concluded that mild or moderate renal impairment had no clinically meaningful impact on the PK of pevonedistat. Although renal clearance of parent drug is only a minor (2.5%) contributor to overall pevonedistat clearance, the possibility of severe renal impairment altering drug metabolism and impacting pevonedistat PK cannot be ruled out.

Azacitidine and its metabolites are primarily excreted by the kidneys. Azacitidine exposures increase (70% following single-dose and 40% following multiple-dose administration) in patients with severe renal impairment. This increase in azacitidine exposure was not correlated with an increase in AEs in the single-agent setting. Therefore, a Cycle 1 dose modification of azacitidine for patient with severe renal impairment is not recommended [10] in its single-agent setting of

approved use. This study will also evaluate the safety of pevonedistat in combination with azacitidine in patients with severe renal impairment.

The effects of severe renal impairment or mild or moderate hepatic impairment on pevonedistat PK will be evaluated in this study. The results of this study will guide development of posology adjustments that may be needed for pevonedistat in these special patient populations. In Part A, administration of a single dose of pevonedistat will allow for the characterization of the effects of severe renal impairment or mild or moderate hepatic impairment on pevonedistat PK. In Part B, the safety and PK of pevonedistat in combination with SOC agents will be assessed. For patients with hematologic malignancies, the PK of both pevonedistat and azacitidine in the combination setting will be assessed. For patients with solid tumors, the PK of pevonedistat will be assessed in the combination setting.

Patients with advanced solid tumors will be eligible for enrollment in the organ impairment arms of the study. Based on the population PK analysis in 416 patients with advanced malignancies, tumor type (hematologic vs solid tumor) did not impact the PK of pevonedistat. Therefore, it is appropriate to broaden participation in this study to include patients with solid tumors. After completing Part A (single dose of pevonedistat), patients with advanced solid tumors will have the option to continue into the second part of the study (Part B), in which they will receive combination treatment with pevonedistat and docetaxel or carboplatin plus paclitaxel.

The choice of the above chemotherapy agents in combination with pevonedistat in this study is based on the following considerations:

- These chemotherapy agents have been well recognized as SOC in a number of malignancies in first-line (carboplatin plus paclitaxel) or in various relapse settings (both regimens).
- The safety profiles, risks, and benefits have been widely studied and reported.
- Additive/synergistic effects of these agents in combination with pevonedistat have been studied in a number of in vitro and in vivo models by the sponsor.

4.3 Rationale for the Dose

Single dose of pevonedistat (Part A)

The recommended clinical dose of pevonedistat as a single agent is 50 mg/m^2 or higher on Days 1, 3, and 5 in 21-day cycles.

In this study, all eligible patients will receive a single dose of 20 mg/m^2 pevonedistat in Part A. A single dose of 20 mg/m^2 pevonedistat in patients with severe renal impairment or mild or moderate hepatic impairment is considered to be safe and is expected to be well-tolerated, as it is at least 2.5-fold below the upper end of the tolerated dose range of single-agent pevonedistat.

Based on the population PK analysis in 416 patients receiving pevonedistat over a dose range of 10 to 278 mg/m^2, levels of ALT and AST did not have meaningful impact on pevonedistat exposures. Tumor type (hematologic vs solid) showed no impact on pevonedistat systemic exposure. In addition, renal clearance plays a minor role in pevonedistat elimination pathways. Patients will be

closely monitored for toxicities. After administration of the first dose of pevonedistat, there will be a period of 4 to 7 days (washout period) without further dosing with pevonedistat.

Multiple dosing of pevonedistat in combination with standard of care agents (Part B)

After completion of Part A, patients will have the opportunity to participate in Part B and receive pevonedistat in combination with SOC agents.

In patients with hematologic malignancies (MDS, CMML, or AML), pevonedistat is being developed in combination with azacitidine. The RP2D is determined to be 20 mg/m^2 on Days 1, 3, and 5 plus 75 mg/m^2 azacitidine on Days 1 through 5, 8, and 9 in 28-day cycles (Study C15009).

In patients with advanced solid tumors, pevonedistat is being developed in combination with carboplatin plus paclitaxel or docetaxel. The RP2D in combination with carboplatin plus paclitaxel is determined to be 20 mg/m^2 on Days 1, 3, and 5 with 175 mg/m^2 paclitaxel plus AUC5 carboplatin on Day 1 in 21-day treatment cycles (Study C15010). The RP2D of pevonedistat in combination with docetaxel is 25 mg/m^2 on Days 1, 3, and 5 with 75 mg/m^2 docetaxel on Day 1 in 21-day treatment cycles (Study C15010).

For patients with normal renal and hepatic function

In patients with hematologic malignancies and normal renal and hepatic function, starting in Cycle 1 of Part B, patients will receive 20 mg/m^2 pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine on Days 1 through 5, 8, and 9 in 28-day cycles.

As of Amendment 02, the Control Arm of the study completed enrollment. Patients with advanced solid tumors with normal renal and hepatic function will not be enrolled in the Control Arm.

For patients with mild hepatic impairment

Three patients with hematologic malignancies and mild hepatic impairment have been enrolled in Study Pevonedistat-1016 and received 10 mg/m^2 pevonedistat in combination with azacitidine. No new safety signals were reported. Therefore, as of Amendment 02, patients with mild hepatic impairment and hematologic malignancies or solid tumors will receive 20 mg/m^2 pevonedistat in combination therapy in Part B.

Starting in Cycle 1 of Part B, patients with hematologic malignancies and mild hepatic impairment will receive 20 mg/m^2 pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles. The starting doses for pevonedistat and azacitidine in combination are not to be escalated in this cohort.

Patients with advanced solid tumors and mild hepatic impairment who are considered to benefit from treatment with pevonedistat in combination with carboplatin plus paclitaxel will receive 20 mg/m^2 pevonedistat on Days 1, 3, and 5 in combination with 135 mg/m^2 paclitaxel plus AUC4 carboplatin on Day 1 of each 21-day treatment cycle.

The dose of paclitaxel (135 mg/m^2) selected for patients with mild hepatic impairment is based on USPI recommendations in patients with bilirubin <2 mg/dL [19] and is not to be escalated.

The lower starting dose of carboplatin (AUC4) is selected to provide a window of safety for patients with mild hepatic impairment. Starting in Cycle 2 or in subsequent cycles, intrapatient dose escalation of carboplatin to AUC5 will be allowed if treatment with AUC4 in Cycle 1 is judged to be safe and tolerable.

According to the docetaxel USPI, patients with bilirubin >ULN or AST or ALT ≥1.5 × ULN should not receive docetaxel. Docetaxel will therefore not be dosed in patients with mild or moderate hepatic impairment.

For patients with moderate hepatic impairment

For patients with moderate hepatic impairment, a lower starting dose of pevonedistat (10 mg/m^2) is selected to provide an adequate safety window for potentially increased pevonedistat exposures in this patient population.

Starting in Cycle 1 of Part B, patients with hematologic malignancies and moderate hepatic impairment will receive 10 mg/m^2 pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles.

Patients with advanced solid tumors and moderate hepatic impairment who are considered to benefit from treatment with pevonedistat in combination with carboplatin plus paclitaxel will receive a starting dose of 10 mg/m^2 pevonedistat on Days 1, 3, and 5 in combination with 90 mg/m^2 paclitaxel plus AUC4 carboplatin on Day 1 of each 21-day treatment cycle.

Following sponsor and investigator discussion of safety data from Cycle 1, patients with moderate hepatic impairment who tolerate pevonedistat well at lower doses may be eligible for intrapatient pevonedistat dose escalation in dose increments of 5 mg/m^2 per cycle starting in Cycle 2 (eg, pevonedistat may be increased to 15 mg/m^2 on Days 1, 3, and 5 of Cycle 2) and in subsequent cycles, to a maximum dose of 20 mg/m^2.

The dose of paclitaxel (90 mg/m^2) selected for patients with moderate hepatic impairment is based on USPI recommendations in patients with bilirubin >2 × ULN [19] and is not to be escalated.

As in patients with mild hepatic impairment, carboplatin dosing will begin at AUC4 for patient safety. Starting in Cycle 2 or in subsequent cycles, intrapatient dose escalation of carboplatin to AUC5 will be allowed if treatment with AUC4 in previous cycles is judged to be safe and tolerable. Dose escalation of carboplatin is not to take place during the same cycle in which pevonedistat dose is escalated.

For patients with severe renal impairment

Renal clearance of pevonedistat is a minor route of elimination. Three patients with hematologic malignancies and severe renal impairment have been enrolled in Study Pevonedistat-1016 and received 10 mg/m^2 pevonedistat in combination with azacitidine. No new safety signals were reported. The safety and preliminary PK data from these 3 patients support a starting dose of 15 mg/m^2 pevonedistat. Therefore, patients with severe renal impairment and hematologic malignancies or solid tumors will receive a starting dose of 15 mg/m^2 pevonedistat in combination therapy in Part B.

Starting in Cycle 1 of Part B, patients with hematologic malignancies and severe renal impairment will receive 15 mg/m^2 pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles.

Patients with advanced solid tumors and severe renal impairment who are considered to benefit from treatment with pevonedistat in combination with carboplatin plus paclitaxel will receive 15 mg/m^2 pevonedistat on Days 1, 3, and 5 in combination with paclitaxel 135 mg/m^2 plus carboplatin AUC4 on Day 1 of each 21-day treatment cycle.

Patients with advanced solid tumors and severe renal impairment may receive pevonedistat in combination with docetaxel. For patients considered to benefit from treatment with pevonedistat plus docetaxel, the starting pevonedistat dose in Cycle 1 will be 15 mg/m^2 in combination with docetaxel 75 mg/m^2.

Following sponsor and investigator discussion of safety data from Cycle 1, patients with severe renal impairment who tolerate pevonedistat well at lower doses may be eligible for intrapatient pevonedistat dose escalation. Starting in Cycle 2 or in subsequent cycles, patients treated with pevonedistat in combination with azacitidine or carboplatin plus paclitaxel may be eligible for intrapatient pevonedistat dose escalation to a maximum dose of 20 mg/m^2.

For patients receiving pevonedistat in combination with docetaxel who tolerate pevonedistat well at lower doses, intrapatient dose escalation of pevonedistat in dose increments of 5 mg/m^2 per cycle is allowed starting in Cycle 2 (eg, pevonedistat may be increased to 15 mg/m^2 on Days 1, 3, and 5 of Cycle 2) and in subsequent cycles, to a maximum dose of 25 mg/m^2.

The dose of paclitaxel (135 mg/m^2) is selected for patient safety, however, as paclitaxel is cleared through the hepatic route, patients with severe renal impairment may be eligible for intrapatient dose escalation to 175 mg/m^2 paclitaxel in Cycle 2 or beyond if the lower dose is well-tolerated in Cycle 1.

The starting dose of carboplatin will be AUC4 to provide a window for patient safety. Starting in Cycle 2 or in subsequent cycles, intrapatient dose escalation of carboplatin to AUC5 will be allowed if treatment with AUC4 in Cycle 1 is judged to be safe and tolerable.

Dose escalation of any SOC agent is not permitted in the same cycle as dose escalation of other SOC agents or of pevonedistat.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 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.

5.1.2 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.

5.1.3 Safety Objective

The safety objective (Part A and Part B) is 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.

5.1.4 Exploratory Objectives

Not applicable.

5.2 Endpoints

5.2.1 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.

5.2.2 Secondary Endpoints

The secondary endpoints are as follows:

- $t_{1/2z}$ of pevonedistat following single- and multiple-dose administration.
- C_{max} of pevonedistat following multiple-dose administration.
- Fraction of unbound drug in plasma (f_u) of pevonedistat.
- C_{max} of azacitidine following multiple-dose administration.
- 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.
- 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} 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 hematologic improvement (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.

5.2.3 Exploratory Endpoints

None.

5.2.4 Safety Endpoints

The safety endpoints are:

- AEs, SAEs, assessments of clinical laboratory values, vital signs measurements, and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

6.0 STUDY DESIGN

6.1 Overview of Study Design

This study is an open-label, multicenter, phase 1/1b, 2-part study of pevonedistat plus select SOC agents in adult patients with hematologic malignancies (HR MDS, HR CMML, AML) or solid tumors with various degrees of renal or hepatic function. Eligible patients include those with

relapsed/refractory MDS, nonproliferative 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. As of Amendment 02, patients will be assigned to 1 of 4 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. As of Amendment 02, 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 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 (75 mg/m^2) on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles. Patients will receive azacitidine SC in Cycle 1. Azacitidine will be given SC or IV during Cycle 2 and beyond. 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

Patients may continue to receive 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 toxicities. 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.

AEs and ECOG 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.

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

6.2 Number of Patients

Approximately 42 patients will be enrolled at 25 to 30 study centers located in the United States (US) and EU. Enrollment is achieved when the first dose of any study drug has been administered.

Patients will be assigned to 1 of 4 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). Patients who are withdrawn from treatment during Part A of the study, will be replaced. Patients who are nonevaluable for PK during Part A may also be replaced.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Part A: Patients will participate in the assessment of pevonedistat PK following a single-dose administration of pevonedistat (4 to 7 days).

Part B: Eligible patients who opt to continue into Part B of the study will receive pevonedistat in combination with SOC agents (azacitidine, docetaxel, or carboplatin plus paclitaxel). Patients may receive combination therapy until they experience symptomatic deterioration or PD, discontinuation for any other reason outlined in Section 9.7, or the study is stopped by the sponsor (eg, if a PTA study becomes available). The maximum duration of treatment is 12 cycles, unless the investigator and sponsor (or designee) agree that a patient would benefit from continued treatment. Patients who continue on treatment after 12 cycles will be permitted to take treatment

breaks, at the investigator's discretion, that are no longer than 4 weeks in duration; treatment breaks may not be taken consecutively. The investigator will confirm patient eligibility for continued treatment upon return from a treatment break (Section 8.3). Patients with hematologic malignancies may be allowed to continue study treatment even if they meet the criteria for PD based only on bone marrow blast counts if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who continue on study under these conditions must be reconsented before continuing study treatment (see Section 9.4.1).

Patients with advanced solid tumors who have achieved clinical benefit from combination therapy (chemotherapy plus pevonedistat) and who have developed intolerance that is reasonably attributable to the chemotherapy after 2 or more cycles may continue on single-agent pevonedistat upon request by the investigator and agreement by the sponsor.

Patients will be followed for 30 (+10) days after the last dose of study drugs or the start of subsequent alternative anticancer therapy to permit detection of any delayed treatment-related AEs.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final analyses for the CSR may be conducted when all patients have had the opportunity to complete Part A and Cycle 1 of Part B of the study. Patients will be followed until they are no longer receiving study drug or the study has been terminated by the sponsor.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Maximum Time Frame Per Individual Patient
• AUC_{∞} following a single dose of pevonedistat in patients with normal renal and hepatic function, severe renal impairment, or mild or moderate hepatic impairment (Part A).	Up to 72 hours following single dose of pevonedistat.
• 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 (Part A).	Up to 72 hours following single dose of pevonedistat.
• 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 (Part A).	Up to 72 hours following single dose of pevonedistat.
• $t_{1/2z}$ of pevonedistat (Parts A and B).	Up to 72 hours following pevonedistat dosing.
• f_u of pevonedistat.	Up to 48 hours following pevonedistat dosing.
• $t_{1/2z}$ of azacitidine (Part B).	Up to 8 hours following azacitidine dosing.
• AUC_{τ} of pevonedistat and azacitidine (Part B).	Up to 48 hours following azacitidine and pevonedistat dosing.
• CL of pevonedistat (Parts A and B).	Up to 72 hours following pevonedistat dosing.
• CL/F of azacitidine.	Up to 8 hours following azacitidine dosing.
• $CL_{R,\ pevonedistat}$ (Part B).	Up to 8 hours following pevonedistat dosing.
• $CL_{R,\ azacitidine}$ (Part B).	Up to 8 hours following azacitidine dosing.
• V_{ss} of pevonedistat (Parts A and B).	Up to 72 hours following pevonedistat dosing.
• V_{ss} of azacitidine (Part B).	Up to 8 hours following azacitidine dosing.
• Measures of disease response (CR or PR for AML and solid tumors; CR, PR, or HI for MDS and CMML); including response rate and duration of response, based on the investigator's assessment (Part B).	Cycle 2, and then every 3rd cycle thereafter, or otherwise as clinically indicated per the discretion of the investigator. After completion of 11 cycles, disease response will be assessed every 6th cycle, or otherwise as clinically indicated. [a]

AML: acute myelogenous leukemia; AUC_{∞}: area under the plasma concentration-time curve from time zero to infinity; AUC_{last}: area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; AUC_{τ}: area under plasma concentration-time curve from time zero to the end of the dosing interval; CL: total clearance; CL/F: apparent clearance; CL_R: renal clearance; C_{max}: maximum observed plasma concentration; CMML: chronic myelomonocytic leukemia; CR: complete response/remission; f_u: fraction of unbound drug in plasma; HI: hematologic improvement; MDS: myelodysplastic syndromes; PR: partial response/remission; $t_{1/2z}$: terminal disposition phase half-life; V_{ss}: volume of distribution at steady-state.

[a] The maximum duration of treatment will be 12 cycles; however, if it is determined after discussion between the investigator and the sponsor that a patient would derive benefit from continued treatment, the patient may remain on the current combination therapy.

6.3.4 Total Study Duration

It is anticipated that overall this study will last for approximately 3.5 years for Part A and Part B combined.

6.3.5 PTA

6.3.5.1 PTA

If a PTA program should become an option for a patient, and if the responsible investigator and the sponsor agree that the patient would derive benefit from or would be harmed without continued treatment, then pevonedistat may be provided through the PTA program (where permitted by local regulations).

6.3.5.2 Duration of PTA

If a PTA program should become an option for a patient, as described in Section 6.3.5.1, the sponsor may continue to provide pevonedistat to that patient through the PTA program. Continued access to pevonedistat for participants will be terminated for those individuals who no longer benefit from treatment (eg, their disease has progressed or treatment is no longer tolerable), the benefit-risk no longer favors the individual, an appropriate alternative therapy becomes available, or pevonedistat becomes available either commercially or via another access mechanism. PTA may be terminated in a country or geographic region where the development of pevonedistat has been suspended or stopped by the sponsor or where pevonedistat can no longer be supplied.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

7.1.1 All Patients

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Male and female patients aged 18 years or older.
2. Expected survival of at least 3 months from the date of enrollment in the study.
3. ECOG PS of 0, 1, or 2 (Appendix D).
4. Recovered (ie, Grade ≤1 toxicity) from the reversible effects of prior anticancer therapy.
5. Prothrombin time (PT) and aPTT ≤1.5 × ULN at screening or within 7 days before the first dose of study drug.
6. Female patients who:
   - Are postmenopausal (see Appendix E) for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - Agree, if they are of childbearing potential, to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix F), at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.

7. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.
8. Suitable venous access for the study-required blood sampling (ie, PK sampling).
9. Voluntary written consent must be given by the patient or the patient's legally acceptable representative before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient or the patient's legally acceptable representative at any time without prejudice to future medical care.

7.1.2 Patients With Hematologic Malignancies

In addition to the inclusion criteria in Section 7.1.1, each patient with hematologic malignancies must also meet the following inclusion criteria, as they apply to their specific malignancy, to be enrolled in the study:

10. Previously untreated hematologic malignancies not suitable for induction therapy.
11. Morphologically confirmed diagnosis of MDS or nonproliferative CMML (ie, with white blood cell [WBC] <13,000/µL) at study entry, based on one of the following:

    French-American-British Classifications [2]:

    - Refractory anemia with excess blasts (RAEB), defined as having 5% to 20% myeloblasts in the bone marrow.
    - CMML with 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood.

    OR

    WHO Classifications [3]:

    - RAEB-1, defined as having 5% to 9% myeloblasts in the bone marrow.
    - RAEB-2, defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood.
    - CMML-2, defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood.

- CMML-1 (although CMML-1 is defined as having <10% myeloblasts in the bone marrow and/or <5% blasts in the blood, these patients may enroll only if bone marrow blasts ≥5%).

12. All patients with MDS or CMML must also have one of the following Prognostic Risk Categories at study entry, based on the Revised International Prognostic Scoring System (IPSS-R) [4]:
    - Very high (>6 points).
    - High (>4.5-6 points).
    - Intermediate (>3-4.5 points): a patient determined to be in the Intermediate Prognostic Risk Category is only allowable in the setting of ≥5% bone marrow myeloblasts.
13. Patients with WHO-defined AML at study entry, including leukemia secondary to prior chemotherapy or resulting from an antecedent hematologic disorder, who have failed to achieve CR or who have relapsed after prior therapy and are not candidates for potentially curative treatment.
14. Patients with relapsed or refractory MDS at study entry, who have previously been treated with an hypomethylating agent.
15. For patients with hematologic malignancies, laboratory value requirements per study arms for eGFR, total bilirubin, and ALT are provided in the table below:

Treatment Arm	eGFR (mL/min/1.73 m^2)	Total Bilirubin	ALT
Control	≥90	≤ULN	≤ULN
Renal	<30	≤ULN	≤2.5 × ULN
Mild hepatic	≥60	ULN <bilirubin ≤1.5 × ULN (not secondary to transfusions)	Any
Moderate hepatic	≥60	1.5 × ULN <bilirubin ≤3.0 × ULN (not secondary to transfusions)	Any

ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate; ULN: upper limit of the normal range.
Refer to Section 9.4.16 for information regarding hepatic and renal function laboratory result requirements.

7.1.3 Patients With Advanced Solid Tumors

In addition to the inclusion criteria in Section 7.1.1, each patient with advanced solid tumors must also meet the following inclusion criteria to be enrolled in the study:

16. Adult patients who have a histologically or cytologically confirmed metastatic or locally advanced solid tumor that is appropriate for treatment with pevonedistat in combination with either docetaxel or carboplatin plus paclitaxel in Part B of this study, or have progressed despite standard therapy, or for whom conventional therapy is not considered effective.
17. For patients with advanced solid tumors, clinical laboratory values are specified below:
    - Hemoglobin ≥8 g/dL. Patients may be transfused to achieve this value.

- For patients to be treated with pevonedistat plus docetaxel in Part B, total bilirubin must be ≤ULN.
- ALT, AST, and ALP ≤2.5 × ULN.
  - For patients to be treated with pevonedistat plus docetaxel in Part B, AST and ALT must be ≤1.5 × ULN. Only patients with severe renal impairment may be considered for this combination.
- ANC ≥1500/mm^3.
- Platelet count ≥100,000/mm^3.
- Albumin ≥2.7 g/dL.

18. Computerized tomography (CT) scan or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis within 28 days of the first dose of study drug.
19. For patients with advanced solid tumors, laboratory value requirements per study arms for eGFR, total bilirubin, and ALT are provided in the table below:

Treatment Arm	eGFR (mL/min/1.73 m^2)	Total Bilirubin	ALT
Renal	<30	≤ULN	≤1.5 × ULN [a] or ≤2.5 × ULN [b]
Mild hepatic [c]	≥60	ULN <bilirubin ≤1.5 × ULN	Any
Moderate hepatic [c]	≥60	1.5 × ULN <bilirubin ≤3.0 × ULN	Any

ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate; ULN: upper limit of the normal range.
Refer to Section 9.4.16 for information regarding hepatic and renal function laboratory result requirements.
[a] For patients who receive pevonedistat plus docetaxel only.
[b] For patients who receive pevonedistat plus carboplatin plus paclitaxel only.
[c] Patients with advanced solid tumors in the hepatic impairment arms will not receive combination treatment with pevonedistat and docetaxel.

7.2 Exclusion Criteria

7.2.1 All Patients

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures or could limit expected patient survival to less than 6 months.
2. End-stage renal disease requiring hemodialysis at study entry.
3. Gilbert syndrome.

4. Treatment with any investigational products or participation in any interventional studies within 21 days before the first dose of any study drug.
5. Known hypersensitivity to pevonedistat or its excipients.
6. Active uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, or septicemia. Prophylactic treatment with antibiotics is allowed.
7. Major surgery within 14 days before first dose or a scheduled surgery during study period; insertion of a venous access device (eg, catheter, port) is not considered major surgery.
8. Life-threatening illness unrelated to cancer.
9. Known HIV seropositive.
10. Known hepatitis B surface antigen seropositive or known or suspected active hepatitis C infection.

    Note: Patients who have isolated positive hepatitis B core antibody (ie, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load.
11. Known hepatic cirrhosis or severe pre-existing hepatic impairment.
12. Known cardiopulmonary disease defined as unstable angina, clinically significant arrhythmia, congestive heart failure (New York Heart Association Class III or IV; see Appendix G), and/or myocardial infarction within 6 months before first dose. However, patients with ischemic heart disease who have had acute coronary syndrome, myocardial infarction, or revascularization more than 6 months before screening and who are without cardiac symptoms may enroll. Patients with congestive heart failure (New York Heart Association Class III or IV) or New York Heart Association Class II with recent decompensation requiring hospitalization within 4 weeks before screening are excluded.
13. Prolonged rate corrected QT interval ≥500 msec, calculated according to institutional guidelines.
14. Treatment with strong CYP3A inducers (see Appendix M) within 14 days before the first dose of pevonedistat.
15. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 of Part A, before first dose of study drug.
16. Female patients who intend to donate eggs (ova) during the course of this study or for 6 months after receiving their last dose of study drug(s).
17. Male patients who intend to donate sperm or father a child during the course of this study or for 4 months after receiving their last dose of study drug(s).
18. Diagnosed or treated for a different malignancy within 2 years before randomization or previously diagnosed with a different malignancy with any current evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not

excluded if they have undergone resection. Patients with AML who have a history of MDS or CMML are not excluded, as MDS/CMML to AML is a natural progression for hematologic disease.

19. High blood pressure that cannot be controlled by standard treatments.
20. Left ventricular ejection fraction (LVEF) <50% within 6 months prior to study enrollment. If a result within this time frame is unavailable, LVEF must be determined by echocardiography or multigated acquisition scan at screening.
21. Severe uncontrolled ventricular arrhythmias or torsade de pointes; electrocardiographic evidence of acute ischemia or active conduction system abnormalities; or clinically significant arrhythmia (as an example, well-controlled atrial fibrillation would not be an exclusion whereas uncontrolled atrial fibrillation would be an exclusion).
22. Severe symptomatic pulmonary hypertension requiring pharmacologic therapy or patients with chronic respiratory disease that requires continuous oxygen.

7.2.2 Patients With Hematologic Malignancies

Patients with hematologic malignancies meeting any of the following additional exclusion criteria are not to be enrolled in the study:

23. Acute promyelocytic leukemia as diagnosed by morphologic examination of bone marrow, by fluorescent in situ hybridization or cytogenetics of peripheral blood or bone marrow, or by other accepted analysis.
24. Patients with AML with a WBC count ≥50,000/μL. Patients who are cytoreduced with leukapheresis or with hydroxyurea may be enrolled if they otherwise meet the eligibility criteria.
25. Patients with either clinical evidence of or history of central nervous system (CNS) involvement by AML.
26. Known hypersensitivity to azacitidine or its excipients.
27. For patients with hematologic malignancies, PT or aPTT >1.5 × ULN or active uncontrolled coagulopathy or bleeding disorder. Patients therapeutically anticoagulated with warfarin, direct thrombin inhibitors, direct factor Xa inhibitors, or heparin are excluded from enrollment.

7.2.3 Patients With Advanced Solid Tumors

Patients with advanced solid tumors meeting any of the following additional exclusion criteria are not to be enrolled in the study:

28. Prior treatment with radiation therapy involving ≥25% of the hematopoietically active bone marrow.
29. Known hypersensitivity or history of severe intolerance or toxicity to chemotherapeutic agents, including known history of severe hypersensitivity reactions to docetaxel (polysorbate 80-based formulations) for patients to be treated with pevonedistat in combination with

docetaxel; history of hypersensitivity to carboplatin for patients to be treated with pevonedistat plus carboplatin plus paclitaxel; or history of severe hypersensitivity to paclitaxel (Cremophor-based formulations) for patients to be treated with pevonedistat with carboplatin plus paclitaxel.

30. CNS metastasis, except for patients who have received prior treatment (radiation or resection) and have stable CNS disease (eg, stable MRI, no steroid requirement).

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

The amount of study drug (pevonedistat and/or azacitidine, docetaxel, or paclitaxel, as applicable) to be administered will be based on body surface area (BSA). BSA will be calculated using a standard formula (see example in Appendix H) on Day 1 of Part A and on Day 1 of each cycle in Part B if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

On days when azacitidine is coadministered with pevonedistat, azacitidine is given first, followed by the pevonedistat IV infusion.

Part A:

All eligible patients will receive a single dose of 20 mg/m^2 pevonedistat via a 1-hour IV infusion on Day 1. There will be no SOC agents administered or additional pevonedistat dosing during Part A.

Part B:

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

Patients With Hematologic Malignancies

Patients with hematologic malignancies may receive pevonedistat on Days 1, 3, and 5 in combination with azacitidine (75 mg/m^2) on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles. Patients will receive azacitidine SC in Cycle 1. Azacitidine will be given SC or IV during Cycle 2 and beyond. On the days both study drugs are administered, azacitidine will be administered first, followed by pevonedistat. 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. The schedule of PK sampling for patients with hematologic malignancies is provided in Appendix A, Table B.

Patients With Advanced Solid Tumors

Patients with advanced solid tumors may receive pevonedistat in combination with docetaxel or with 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 PK sampling for patients with solid tumors is provided in Table D of Appendix A.

For patients with solid tumors and severe renal impairment, the investigator will select which chemotherapy (docetaxel or carboplatin plus paclitaxel) each patient will receive in combination with pevonedistat based on his/her medical judgment and indication provided in package inserts (USPI/SmPC).

Starting Doses for Patients With Organ Impairment

Following sponsor and investigator discussion of safety data from Cycle 1, patients in the organ impairment arms who tolerate pevonedistat well at lower doses may be eligible for intrapatient dose escalation in Part B, starting in Cycle 2 or soon thereafter. The maximum dose of pevonedistat that may be administered in combination with azacitidine or carboplatin plus paclitaxel is 20 mg/m^2. The maximum dose of pevonedistat that may be administered in combination with docetaxel is 25 mg/m^2. Patients with advanced solid tumors may also be eligible for intrapatient dose escalation of SOC agents, depending on the study arm in which they are enrolled. Starting doses and intrapatient dose escalation guidelines for patients with organ impairment are described in Table 8.a, Table 8.b, and Table 8.c.

Table 8.a Starting Doses for Patients With Mild Hepatic Impairment

Malignancy	Pevonedistat [a] (mg/m^2)	Azacitidine [b] (mg/m^2)	Paclitaxel [c] (mg/m^2)	Carboplatin [d]
Hematologic	20	75	-	-
Solid tumors	20	-	135	AUC4

AUC: area under the plasma concentration-time curve.

[a] The maximum dose of pevonedistat that may be administered in combination with azacitidine or carboplatin plus paclitaxel is 20 mg/m^2.

[b] The maximum dose of azacitidine that may be administered in combination with pevonedistat is 75 mg/m^2.

[c] The maximum dose of paclitaxel that may be administered in combination with pevonedistat and carboplatin is 135 mg/m^2.

[d] Following sponsor and investigator discussion of the available safety data, patients who tolerate treatment well at the initially assigned dose of carboplatin may be allowed to increase their dose to a maximum dose of AUC5 during Cycle 2 or in subsequent cycles of treatment.

Table 8.b Starting Doses for Patients With Moderate Hepatic Impairment

Malignancy	Pevonedistat [a] (mg/m^2)	Azacitidine [b] (mg/m^2)	Paclitaxel [c] (mg/m^2)	Carboplatin [d]
Hematologic	10	75	-	-
Solid tumors	10	-	90	AUC4

AUC: area under the plasma concentration-time curve.

[a] 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 in increments of 5 mg/m^2 per cycle starting in Cycle 2 (eg, pevonedistat at 15 mg/m^2 on Days 1, 3, and 5 of Cycle 2). The maximum dose of pevonedistat that may be administered in combination with azacitidine or carboplatin plus paclitaxel is 20 mg/m^2.

[b] The maximum dose of azacitidine that may be administered in combination with pevonedistat is 75 mg/m^2.

[c] The maximum dose of paclitaxel that may be administered in combination with pevonedistat and carboplatin is 90 mg/m^2.

[d] Following sponsor and investigator discussion of the available safety data, patients who tolerate treatment well at the initially assigned dose of carboplatin may be allowed to increase their dose to a maximum dose of AUC5 during Cycle 2 or in subsequent cycles of treatment. Intrapatient dose escalation of carboplatin is not to take place during the same cycle in which pevonedistat dose is escalated.

Table 8.c Starting Doses for Patients With Severe Renal Impairment

Malignancy	Pevonedistat (mg/m^2)	Azacitidine [a] (mg/m^2)	Paclitaxel [b] (mg/m^2)	Carboplatin [c]	Docetaxel [d] (mg/m^2)
Hematologic	15 [e]	75	-	-	-
Solid tumors [f]	15 [g]	-	135	AUC4	
Solid tumors [f]	15 [g]				75

AML: acute myelogenous leukemia; AUC: area under the plasma concentration-time curve; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes; SOC: standard of care.

Note: **Dose escalation of any SOC agent is not permitted in the same cycle as dose escalation of other SOC agents or of pevonedistat. Only 1 study drug may be escalated in a cycle.**

[a] The maximum dose of azacitidine that may be administered in combination with pevonedistat is 75 mg/m^2.

[b] Following sponsor and investigator discussion of the available safety data, patients who tolerate treatment well at the initially assigned dose of paclitaxel may be allowed to increase their dose to a maximum dose of 175 mg/m^2 in Cycle 2 or in subsequent cycles.

[c] Patients who tolerate treatment well at the initially assigned dose of carboplatin may be allowed to increase their dose to a maximum dose of AUC5 in Cycle 2 or in subsequent cycles.

[d] The maximum dose of docetaxel that may be administered in combination with pevonedistat is 75 mg/m^2. Patients receiving pevonedistat plus docetaxel may have a maximum of 2 docetaxel dose modifications, with dose reductions to 60 mg /m^2 or 45 mg/m^2 allowed.

[e] Patients with hematologic malignancies who tolerate treatment well at the initially assigned dose of pevonedistat may be allowed to increase their dose to a maximum of 20 mg/m^2 starting in Cycle 2.

[f] For patients with solid tumors and severe renal impairment, the investigator will select which chemotherapy (docetaxel or carboplatin plus paclitaxel) that each patient will receive in combination with pevonedistat based on his/her medical judgment.

[g] Patients with advanced solid tumors who tolerate treatment well at the initially assigned dose of pevonedistat may be allowed to increase their dose in increments of 5 mg/m^2 per cycle starting in Cycle 2 (eg, pevonedistat at 20 mg/m^2 on Days 1, 3, and 5 of Cycle 2). The maximum dose of pevonedistat that may be administered in combination with carboplatin plus paclitaxel is 20 mg/m^2. The maximum dose of pevonedistat that may be administered in combination with docetaxel is 25 mg/m^2.

Study drugs will be administered per the instructions for dosing in Section 8.1.1, Section 8.1.2, and Section 8.1.3.

8.1.1 Instructions for Pevonedistat and Azacitidine Dosing

Patients will receive pevonedistat diluted with 5% dextrose or 0.9% saline solution in a 250 mL bag via a 60-minute IV infusion per the information provided in the Directions for Investigational Drug Use document located in the Pharmacy Manual. Pevonedistat should be administered through central or peripheral venous access. The infusion may be slowed or stopped and restarted for any associated infusion-related reactions. All infusion times must be recorded. The total time from drug reconstitution to end of infusion must not exceed 6 hours.

The entire content of the pevonedistat IV bag will be infused at a constant rate over 60 (±10) minutes. The start and end time of IV infusion should be recorded accurately, particularly when PK assessments are performed. To ensure that all the pevonedistat is administered, the infusion line will be flushed with 0.9% saline solution or 5% dextrose immediately after

administration. The volume used for line flushing is not considered a part of the volume of the pevonedistat IV bag to be documented.

On Days 1, 3, and 5, when both study drugs are administered, azacitidine will be administered-first followed by pevonedistat. The infusion of pevonedistat will begin between 15 and 60 minutes after completion of administration of azacitidine.

8.1.2 Instructions for Pevonedistat and Docetaxel Dosing

On Day 1 of each cycle in Part B, docetaxel 75 mg/m^2 will be administered as a 1-hour IV infusion and pevonedistat will be administered as described in Section 8.1.1. On Days 3 and 5, only pevonedistat will be given. The duration of each cycle will be 21 days. Refer to the most recent USPI/SmPC for further details regarding docetaxel administration [13,20].

Premedication to prevent docetaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. For example, patients may be treated with dexamethasone (4 mg twice daily for 3 days), which should start 24 hours before docetaxel administration.

8.1.3 Instructions for Pevonedistat and Carboplatin Plus Paclitaxel Dosing

On Day 1 of each cycle in Part B, paclitaxel will be given as an IV infusion over approximately 3 hours, followed by carboplatin as an approximately 30-minute IV infusion. Pevonedistat will be administered as described in Section 8.1.1. On Days 3 and 5, only pevonedistat will be given. The duration of each cycle will be 21 days.

- Refer to the most recent SmPC/USPI for further details regarding carboplatin administration [14,15].

  If a patient's GFR is estimated using serum creatinine measurements by the standardized isotope dilution mass spectrometry method, the US Food and Drug Administration (FDA) recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Using the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

  Total carboplatin dose (mg) = (target AUC) × (GFR + 25) [Calvert formula]

  Maximum carboplatin dose (mg) = target AUC (mg × min/mL) × (150 mL/min)

  The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

  For a target AUC = 4, the maximum dose is 4 × 150 = 600 mg.

  For a target AUC = 5, the maximum dose is 5 × 150 = 750 mg.

- Refer to the most recent SmPC/USPI for further details regarding paclitaxel administration [17,19].

Premedication to prevent paclitaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. For example, patients may be treated with either dexamethasone (10 mg) 24 hours before and on the day of paclitaxel dosing or methylprednisolone immediately before paclitaxel dosing.

8.2 Reference/Control Therapy

Not applicable.

8.3 Dose Modification Guidelines

8.3.1 Dose Modifications for Hematologic Toxicities

8.3.1.1 Pevonedistat

It is not anticipated that pevonedistat dose modifications would be necessary because of myelosuppression. However, if clinically indicated in the opinion of the investigator, the pevonedistat dose may be reduced by 1 dose level (eg, from 20 mg/m^2 to 15 mg/m^2 or 10 mg/m^2). The pevonedistat dose may be re-escalated to 15 mg/m^2 or 20 mg/m^2 at a subsequent cycle, if the toxicity has recovered to Grade ≤1 or the patient's baseline.

Although leukostasis is not anticipated in this study, pevonedistat should be held for symptoms of leukostasis until the leukostasis is treated per institutional guidelines. Pevonedistat may be restarted when WBC count is <50,000/µL and following agreement by the sponsor's project clinician (or designee).

8.3.1.2 Azacitidine

Dose reduction or delays of azacitidine for hematologic toxicities (including fever and neutropenia) should be strongly discouraged, as it may impact patient outcome.

In Part B, combination treatment with pevonedistat and azacitidine will be repeated every 28 days for patients with hematologic malignancies. For patients with Grade 4 neutropenia at risk of infection, particularly in a relapse/refractory setting, prophylactic administration of antibacterial or antifungal agents may be considered, as appropriate, per medical judgment of treating physician or per institutional guidelines. In addition, administration of granulocyte colony stimulating factor (G-CSF) prior to and during study may be considered as appropriate, per medical judgment of treating physician or per institutional guidelines.

For patients with Grade 4 neutropenia, particularly in a relapse/refractory setting, the start of a new treatment cycle may be delayed if failure to recover counts is thought to be related to marrow replacement with blasts. For patients with delays in the initiation of a new cycle of treatment due to toxicity, for therapy to resume, toxicity considered related to treatment must have resolved to the patient's baseline values, or to a level considered acceptable by the investigator after discussion with the project clinician or designee.

Initiation of the next cycle of treatment may be delayed for up to 2 weeks. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. Should treatment need to be delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, then the azacitidine dose will be decreased to 50 mg/m^2 when treatment is resumed.

If the reduced dose is well tolerated and the toxicity leading to dose reduction was Grade ≤3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor's project clinician (or designee).

A delay in the initiation of a cycle by 4 weeks or greater because of lack of recovery from treatment-related hematologic toxicity to the patient's baseline values, or to a level considered acceptable by the investigator after discussion with the project clinician (or designee) that is not related to leukemic infiltration, will trigger consideration for discontinuation of the patient from the study. If hematologic toxicity has not resolved by 6 weeks, the patient must be discontinued from the study.

If indicated, bone marrow evaluation will be performed to establish whether continued myelosuppression is related to persistent or progressing leukemic infiltration.

8.3.1.3 Docetaxel, Carboplatin, and Paclitaxel

Dose modification guidelines for specific hematologic toxicities in patients with advanced solid tumors receiving docetaxel or carboplatin/paclitaxel in Part B are presented in Table 8.d.

Patients with unresolved toxicities of Grade >1 lasting 3 weeks or longer from the date of the next scheduled treatment will be discontinued from the study. For detailed dose modification guidelines, see Section 8.3.2.3.

Table 8.d Dose Modification Guidelines for Specific Hematologic Toxicities in Patients With Advanced Solid Tumors

Pathologic Condition	Severity	Action on Study Drug
Hematologic: ANC	Febrile neutropenia	Hold dosing on Day 1 of Cycles ≥2 up to 3 weeks until febrile neutropenia is resolved, then resume dosing as appropriate. Consider use of growth factor or reduce chemotherapy by 1 dose level, as appropriate.
	ANC <1500 cells/μL on Day 1 of Cycles ≥2	Initiation (Day 1) of Cycles ≥2 should be delayed for up to 3 weeks until ANC is ≥1500 cells/μL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
	Grade ≥3 neutropenia lasting >7 days	Initiation (Day 1) of Cycles ≥2 should be delayed until ANC is ≥1500 cells/μL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
Hematologic: Platelets	Platelet count <100,000/μL on any dosing day of Cycles ≥2	Dosing in Cycles ≥2 should be delayed for up to 3 weeks until platelet count is ≥100,000 cells/μL. Dose of chemotherapy may be reduced by 1 dose level as appropriate.
	Grade 4 thrombocytopenia lasting >7 days or platelet count <25,000 cells/μL at any time	Dosing in Cycles ≥2 should be delayed until platelet count is ≥100,000 cells/μL (see Section 8.3.2.3). Dose of chemotherapy may be reduced by 1 dose level as appropriate.
Hematologic: Anemia	Grade ≥1	No dose modification is allowed for anemia. Transfusion and/or erythropoietin may be given, as clinically indicated, for the treatment of anemia (see Section 8.7.1.1).

ANC: absolute neutrophil count.

8.3.2 Dose Modifications for Nonhematologic Toxicities

8.3.2.1 Pevonedistat

Pevonedistat Dose Adjustment Based on Serum Transaminases and Total Bilirubin

Transient ALT/AST elevations have been observed in some patients (approximately 5% to 8% in patients with AML/MDS and approximately 20% in patients with solid tumors) after pevonedistat dosing. For patients with increased liver function tests (compared to baseline) on Day 3 or Day 5, pevonedistat dosing should be held; once the elevated AST or ALT returns to the patient's baseline level or better, and/or elevated bilirubin returns to patient's baseline level or better, pevonedistat dose may be resumed.

Pevonedistat Dose Adjustment Based on Hypophosphatemia

If hypophosphatemia is Grade ≥3, study drug treatment should not be resumed until the hypophosphatemia is Grade ≤2. Hypophosphatemia should be evaluated (including severity and etiology), monitored, and treated according to institutional guidelines.

Pevonedistat Dose Adjustment for Other Toxicities

For other Grade ≥2 nonhematologic toxicities potentially related to pevonedistat, the pevonedistat dose may be reduced from 20 mg/m^2 to 15 mg/m^2 or 10 mg/m^2 at the discretion of the investigator as clinically indicated. If the toxicity returns to Grade ≤1 or the patient's baseline status, pevonedistat may be re-escalated to 15 mg/m^2 or 20 mg/m^2 at the next cycle.

8.3.2.2 Azacitidine

Azacitidine Dose Adjustment Based on Renal Function and Serum Electrolytes (Mild or Moderate Hepatic Impairment and Control Arms Only)

For renal toxicities, specifically elevated creatinine Grade >1, azacitidine should be reduced in accordance with the prescribing information [10] and/or institutional guidelines. Similarly, if unexplained elevations in serum creatinine or blood urea nitrogen occur, the next cycle should be delayed until values return to normal or baseline values, and the dose should be reduced by 50% on the next treatment course.

If unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, the azacitidine dose should be reduced by 50% on the next course. The azacitidine dose may be re-escalated back to 75 mg/m^2 at the next cycle if the toxicity has recovered to Grade ≤1 or the patient's baseline status.

8.3.2.3 Docetaxel, Carboplatin, and Paclitaxel

Criteria for Beginning or Delaying a Subsequent Treatment Cycle

For individual patients experiencing specific toxicities, treatment in each new cycle will be delayed until toxicity is reduced to Grade ≤1, patient's baseline, or to a level considered acceptable by the investigator after discussion with the project clinician or designee.

If dosing with pevonedistat is held for toxicity during any given cycle, dosing may resume within that same cycle when toxicity is resolved. Alternatively, dosing may be held until the next cycle. The start of the next cycle may also be delayed for up to 3 weeks to allow patients to recover from any safety concerns, so that pevonedistat may be administered in combination with chemotherapy.

Day 1 dosing of any cycle in Part B may be delayed by up to 2 days to accommodate inclement weather, holidays, vacations, or other administrative reasons.

Criteria for Dose Interruption During a Cycle

During treatment with SOC agents, the infusion may be slowed or stopped and restarted for any associated infusion-related reactions. The exact date and time of each additional sample collection and the actual start and stop times of the infusion should be recorded accurately.

Criteria for Dose Reduction

Alopecia of any duration will not lead to dose modification or treatment delay.

Patients receiving pevonedistat plus docetaxel may have a maximum of 2 docetaxel dose modifications. Docetaxel is initially dosed at 75 mg/m^2, dose reductions up to 60 mg /m^2 and

45 mg/m^2 may be considered (if applicable) or pevonedistat may be modified as described in Section 8.3.2.1.

The decision to treat at a reduced dose level of chemotherapy is at the discretion of the investigator. Discussions with the project clinician or designee are encouraged.

Criteria for Discontinuation of Study Drug

Patients receiving pevonedistat plus docetaxel who require more than 2 dose modifications of either docetaxel or pevonedistat will be discontinued from the study.

Patients receiving pevonedistat and carboplatin plus paclitaxel may have no more than 1 dose modification (if applicable) of chemotherapy agents or of pevonedistat (see above). Patients who require additional dose modifications will be discontinued from the study.

Dose modification guidelines for specific nonhematologic toxicities in patients with advanced solid tumors are presented in Table 8.e. Treatment cannot be withheld for longer than 3 weeks for any toxicity Grade >1.

Table 8.e Dose Modification Guidelines for Specific Nonhematologic Toxicities in Patients With Advanced Solid Tumors

Pathologic Condition	Severity	Action on Study Drug
Nausea, emesis, or diarrhea despite maximal prophylaxis	Grade ≥3	On days when both chemotherapy and pevonedistat are administered, hold dosing for up to 3 weeks or until the toxicity returns to Grade ≤1, then restart at the next lower dose of chemotherapy. On days when pevonedistat is given as a single agent, hold pevonedistat dosing for up to 3 weeks or until the toxicity returns to Grade ≤1 before dosing is resumed. **Note**: Ensure that optimal prophylaxis has been employed before dose reduction. Supportive care should be considered per local institutional guidelines, as clinically indicated.
Neurotoxicity (paclitaxel or docetaxel only)	Grade ≥2	Hold treatment until patient recovers to Grade 1 toxicity, then resume treatment at the next lower dose level. This will be a permanent dose reduction. Carboplatin or pevonedistat dose is not to be modified.
Allergic reaction (paclitaxel or docetaxel only	Moderate symptoms	Stop infusion. Give IV diphenhydramine 25 to 50 mg, IV dexamethasone 10 mg, and/or treatment per institutional guidelines. After recovery of symptoms, resume infusion at a low infusion rate. If no further symptoms occur, resume full dose rate until infusion is complete. If symptoms recur, stop infusion and discontinue patient from the study.

IV: intravenous.

8.3.3 Intrapatient Dose Escalation (Part B)

In Part B, following sponsor and investigator discussion of the patient's safety and tolerability data from Cycle 1, patients in the organ impairment arms who tolerate pevonedistat well at the initially

assigned dose may be allowed to increase their dose of pevonedistat in increments of 5 mg/m^2 per cycle during Cycle 2 or in subsequent cycles of treatment. Patients with advanced solid tumors who tolerate initial doses of SOC agents may also be allowed to increase their dose of SOC agents, depending on the allowances of their study arm and only in cycles in which their dose of pevonedistat is not increased. Starting doses and intrapatient dose escalation plans for study drugs in each organ impairment arm are presented in Table 8.a, Table 8.b, and Table 8.c.

8.4 Excluded Concomitant Medications and Procedures

Prohibited concomitant therapies include investigational agents, androgens, supraphysiologic doses of corticosteroids, erythropoietin, thrombopoietin agonists (eg, eltrombopag and romiplostim), or chemotherapeutic agents active against hematologic malignancies or advanced solid tumors.

Results from Study C15011 indicated that itraconazole, a strong CYP3A/ P glycoprotein (P-gp) inhibitor, and fluconazole, a moderate CYP3A inhibitor, had no clinically meaningful effects on pevonedistat PK. The effect of rifampin, a strong CYP3A inducer, on pevonedistat PK was evaluated in Study P1015. The geometric mean AUC_∞ of pevonedistat in the presence of rifampin was 79% of that in the absence of rifampin (90% CI: 69.2%, 90.2%). The result indicated that coadministration of rifampin did not result in clinically meaningful alteration of pevonedistat systemic exposures in the context of 28% of inter-individual variability in pevonedistat clearance. In order to interpret the effects of organ impairment on pevonedistat PK without potential confounding factors, strong CYP3A inhibitors and inducers remain prohibited in this study.

A physiologically based PK (PBPK) model accounting for hepatic uptake and metabolism of pevonedistat was developed to describe the PK of pevonedistat and the observed low sensitivity to DDIs with strong CYP3A/P-gp inhibitor (itraconazole) and strong inducer (rifampin). The pevonedistat PBPK model indicates that the systemic exposure of pevonedistat was not sensitive to the perturbations of enzyme activity when the hepatic uptake becomes the rate-determining step of its clearance. Considering the minimum effect on P-gp inhibition and hepatic uptake being the rate-determining step of pevonedistat clearance, the effect of breast cancer resistance protein (BCRP) inhibition on pevonedistat systemic clearance is not expected to be clinically meaningful. Therefore, exclusion of BCRP inhibitors (eg, cyclosporine) is not deemed warranted in clinical studies of pevonedistat and, as of Amendment 02, BCRP inhibitors are no longer included in the list of excluded concomitant medications.

Medications that are generally excluded but are allowed with certain exceptions are listed in Table 8.f (for the combination pevonedistat plus SOC agents).

Table 8.f Concomitant Medications Excluded While Receiving Study Treatment: Combination Pevonedistat Plus SOC agents

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products.	Acetaminophen and acetaminophen-containing compounds may be used judiciously and should not exceed a dose of 2 g of acetaminophen in a 24-hour period.
Systemic antineoplastic therapy, except for hydroxyurea.	Hydroxyurea dosing prior to and during the study treatment phase may be used and adjusted to control the level of circulating blast counts to no lower than 10,000/µL while on study treatment. The dosing of hydroxyurea and changes to dosing of hydroxyurea must be recorded.
Strong CYP3A inhibitors and inducers (see Appendix M)	
Any investigational agent for MDS, CMML, or AML, or commercially available agents used in MDS, CMML, or AML, including androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate].	

AML: acute myelogenous leukemia; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes; SmPC: Summary of Product Characteristics; USPI: United States Prescribing Information.
This list is not all-inclusive; consult the docetaxel, carboplatin, azacitidine, or paclitaxel USPIs or SmPCs, as applicable, for additional information regarding precautions, warnings, and contraindications.

8.5 Permitted Concomitant Medications and Procedures

Medications and procedures that are specifically permitted during the study are listed in Table 8.g.

Table 8.g Concomitant Medications and Procedures Permitted During the Study

Therapy	Comment
Antiplatelet agents (eg, aspirin, clopidogrel) and anticoagulants	May be used in patients who develop a thrombosis while on study. Note that patients with active uncontrolled coagulopathy or who are therapeutically anticoagulated with warfarin, direct thrombin inhibitors, direct Xa inhibitors or heparin are excluded from enrollment as per Section 7.2.
Antiemetics	May be administered according to institutional guidelines.
Antibacterial or antifungal agents	For patients with Grade 4 neutropenia, (defined as ANC ≤500/µL for 7 days or with fever), particularly in relapse/refractory setting, at risk of infection, prophylactic treatment with antibiotics (eg, fluoroquinolone, ciprofloxacin), antifungals (eg, voriconazole, fluconazole, parconazole), and antiviral agents (eg, acyclovir, entecavir, tenofovir) should be initiated, and continued at least through Cycle 1, or per institutional guidance.
Myeloid growth factors (eg, G-CSF, GM-CSF)	In general, the use of myeloid growth factors in patients with myeloid malignancies is discouraged and should be restricted. For patients with myeloid malignancy in CR, CRi, or marrow CR (MLFS), growth factors may be used in specific circumstances, per institutional guidelines and after discussion with the project clinician (or designee). Additionally, to avoid dose delays, patients who experience Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) with or without fever may receive G-CSF or GM-CSF between days 28 through 42 after discussion and agreement with the project clinician (or designee).
Nephrotoxic medications, including nonsteroidal anti-inflammatory drugs	Caution should be used with nephrotoxic concomitant medications (see Appendix K). Alternative concomitant nonnephrotoxic medications should be used whenever possible.
Platelet transfusion	Permitted as medically necessary per institutional guidelines (eg, for platelets <10,000/µL in the absence of clinical bleeding); see Section 8.7.
Red blood cell transfusion	To be considered for all patients with anemia, especially those with hemoglobin values ≤8 g/dL; see Section 8.7. When RBC transfusion is considered, it should be administered at least 1 day prior to dosing with pevonedistat. All incidences of transfusions (and units given) should be captured in the eCRF.

ANC: absolute neutrophil count; CR: complete response/remission; CRi: complete remission with incomplete blood count recovery; eCRF: electronic case report form; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte macrophage colony-stimulating factor; MLFS: morphologic leukemia-free state; RBC: red blood cell.

8.6 Precautions and Restrictions

Concomitant medications and procedures that are excluded or must be used with caution are described in Section 8.4 and Section 8.5, respectively.

Certain situations may warrant further caution, such as modifying the dose of study drug(s). Dose modification guidelines are provided in Section 8.3.

Refer to the package insert for VIDAZA USPI [10] or EU SmPC [11] for precautions and restrictions related to azacitidine use. Refer to the most recent SmPCs/USPIs for further details regarding administration of docetaxel, carboplatin, and paclitaxel.

It is not known what effects pevonedistat has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use highly effective methods of contraception (see list provided in Appendix F) through defined periods during and after study treatment as specified below.

Female patients must meet one of the following criteria:

- Be postmenopausal (see definition in Appendix E) for at least 1 year before the screening visit, OR
- Be surgically sterile, OR
- Agree, if they are of childbearing potential, to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through 6 months after the last dose of study drug (whichever is longer), OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.
- Agree to not donate eggs (ova) during the course of this study or for 6 months after receiving their last dose of study drug(s).

Female patients should be advised not to breastfeed while undergoing treatment with azacitidine.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to one of the following:

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.

Male patients must agree to not donate sperm or father a child during the course of this study or for 4 months after receiving their last dose of study drug(s).

Before starting treatment, male patients should be advised to seek counseling on sperm storage, and female patients should be advised to seek counseling on egg storage.

Nonclinical data suggest that male and female patients administered pevonedistat have a potential risk of infertility.

8.7 Management of Clinical Events

Patients who experience an AE with pevonedistat should be followed closely for a recurrence of similar or other AEs upon subsequent dosing of pevonedistat.

8.7.1 Combination Pevonedistat Plus Standard of Care Agents

Common AEs reported for patients receiving the combination of pevonedistat with specific chemotherapeutic agents are provided in the most recent IB. For the combination of pevonedistat with SOC agents, follow the guidance in the following subsections of this protocol.

8.7.1.1 Guidance for Clinical Assessment and Management of Hemodynamic Compromise (All Patients)

It is essential that the patients receiving the combination of pevonedistat and SOC agents are carefully evaluated at screening and before each dose of study drug for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be given to fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Patients who experience an untoward reaction with the combination of pevonedistat and SOC agents should be followed closely on subsequent dosing.

For patients for whom there is a concern of dehydration, the following guidance for rehydration before pevonedistat dosing may be considered: 500 mL/hr of 0.5 N saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate; each infusion of IV fluids should be recorded in the electronic case report forms (eCRFs).

For all patients with anemia, and especially for those with hemoglobin values ≤8 g/dL at screening or during the conduct of the study, RBC transfusions should be considered before pevonedistat dosing based on the risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines. Similarly, for patients with clinically significant thrombocytopenia, especially those with platelet count <10,000/μL, a platelet transfusion should be considered. Any RBC or platelet transfusion must be recorded in the eCRFs.

Patients who experience signs and symptoms of hemodynamic compromise after pevonedistat dosing (eg, tachycardia, hypotension, orthostasis, changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care, including hospitalization, as clinically indicated.

8.7.1.2 Guidance for Management of Cytopenia and Infection (Patients with Hematologic Malignancies)

Cytopenia is common in patients with MDS, CMML, and AML. Patients with baseline neutropenia or those who have significant bone marrow involvement may be at particularly high risk. Patients receiving the combination of pevonedistat and azacitidine are carefully evaluated at screening and before each dose of study drug for neutropenia and risk of infection and provided adequate prophylaxis as outlined below:

- If indicated, bone marrow evaluation will be performed to establish whether continued myelosuppression is related to persistent or progressing leukemic infiltration. When deciding on dose modifications for management of myelosuppression, consider dose modification of azacitidine first before modifications of pevonedistat. Pevonedistat is generally not associated with myelosuppression.
- As general guidance for patients with, or who are expected to experience, significant protracted neutropenia (defined as ANC ≤500/μL for 7 days or with fever) who are therefore at high risk of infection, prophylactic treatment with antibiotics should be initiated as detailed in Table 8.g. Use of anti-infective agents are to be captured in the eCRF.
- In general, the use of myeloid growth factors is discouraged and should be restricted. For patients in CR, CRi, or marrow CR (morphologic leukemia-free state), growth factors may be used in specific circumstances, as detailed in Table 8.g.

8.7.1.3 Guidance Management of Leukostasis (Patients with Hematologic Malignancies)

Pevonedistat treatment should be withheld for patients who develop symptoms of leukostasis. Treatment may include leukapheresis and hydroxyurea administration, per institutional guidelines. When the patient's WBC count is <50,000/μL and symptoms are improved, pevonedistat treatment may be restarted after consulting with the sponsor's project clinician (or designee). Treatment with other chemotherapeutic agents may continue as clinically indicated.

8.7.1.4 Guidance for Management of Extravasation (All Patients)

Based on nonclinical findings as detailed in the IB, pevonedistat is considered a nonvesicant drug. Although no published guidelines are available for extravasation of nonvesicants, the investigator is encouraged to follow institutional guidelines. Some general advice in case of extravasation includes immediately stopping drug infusion and elevating the affected limb to minimize swelling.

8.7.1.5 Guidance for Use of Granulocyte-Colony Stimulating Factor (Patients with Advanced Solid Tumors)

Use of growth factors such as G-CSF in patients with advanced solid tumors are permitted at the investigator's discretion.

8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of Investigational Agents

Upon receipt of drug supply, contents must be verified promptly and the proper contacts notified of any discrepancies or damages as described in the Study/Pharmacy Manual.

8.9.1 Azacitidine

Azacitidine may be supplied by the site from commercial sources, depending on regional availability. Commercially available azacitidine is supplied as lyophilized powder in 100 mg single-use vials. Refer to the Study/Pharmacy Manual and the VIDAZA USPI [10] or EU SmPC [11], as applicable, for additional information regarding azacitidine.

8.9.2 Pevonedistat

The drug product is labeled Pevonedistat (TAK-924/MLN4924) Injection for Solution for Infusion.

Pevonedistat Injection for Solution for Infusion will be supplied by the sponsor as detailed in the Study/Pharmacy Manual.

Each Pevonedistat Injection for Solution for Infusion vial contains 50 mg or 44 mg pevonedistat, as free base, formulated with the following excipients: citric acid (anhydrous), trisodium citrate dihydrate, betadex sulfobutyl ether sodium (Captisol), and water for injection.

Details are available in the IB.

8.9.3 Docetaxel, Carboplatin, and Paclitaxel

Docetaxel, carboplatin, and paclitaxel are each obtained from commercial sources according to local practice standards and are provided as commercially available dose formulations. Additional details are provided in the USPI/SmPC for each agent.

8.10 Preparation, Reconstitution, and Dispensation

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

Before use, Pevonedistat Injection for Solution for Infusion vials should be brought to ambient conditions (15°C-30°C) by removing the vials from the refrigerator and placing them at room temperature. Accelerated warming methods, such as a water bath, must not be used. Pevonedistat Injection for Solution for Infusion is stable at ambient temperature for 6 hours before dilution. If the drug product vial is not to be used within the 6-hour timeframe, the vial should be returned to storage. Each vial is for single use only.

Each Pevonedistat Injection for Solution for Infusion vial contains nominally 5 mL (50 mg) or 4.4 mL (44 mg) pevonedistat, as free base. Before injecting the drug product into the 250 mL IV bag containing a 5% dextrose or 0.9% saline solution, calculate the volume of drug product that will be administered and remove this volume from the 250 mL IV bag containing a 5% dextrose or 0.9% saline solution (see Pharmacy Manual for details). Using sterile technique, withdraw the

appropriate volume of drug from the vial(s) and inject into the 250 mL IV bag containing a 5% dextrose or 0.9% saline solution. The bag must be gently inverted repeatedly to mix the contents. The prepared pevonedistat IV bag must be used within 6 hours if stored at room temperature or must be discarded. Alternatively, the prepared IV bag is chemically stable and may be stored for up to 18 hours at 2°C to 8°C. After 18 hours of storage at 2°C to 8°C, the prepared IV bag must be used within 3 hours upon coming to room temperature or must be discarded.

Discard bag, needle, and syringe in a proper biohazard container according to institutional guidelines.

Detailed reconstitution and dosage preparation instructions are provided in the Directions for Use located in the Pharmacy Manual.

Instructions for the preparation, reconstitution, and dispensation of azacitidine are provided in the VIDAZA USPI [10] or EU SmPC [11]. For instructions and precautions regarding preparation of docetaxel, carboplatin, and paclitaxel, refer to the applicable USPI/SmPC for each agent.

Pevonedistat is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling pevonedistat.

8.11 Packaging and Labeling

Pevonedistat Injection for Solution for Infusion will be provided in United States Pharmacopeia (USP) Type I glass vials. Each USP Type I glass vial nominally contains 5 mL or 4.4 mL of compounded sterile solution, sealed with a chloro-butyl rubber stopper and oversealed with an aluminum seal and a plastic cap.

Azacitidine is available as lyophilized powder in 100 mg, single-use vials from commercial supply with commercial packaging and labeling. Azacitidine may be sourced locally by the clinical sites when regulations allow for clinical site sourcing with appropriate labeling.

Docetaxel, carboplatin, and paclitaxel may be sourced locally by the clinical site when arrangements have been made and agreed to by the sponsor and when regulations allow for clinical site sourcing, appropriate labeling, and compliance with local and regional regulations. As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator and detailed in the Study Manual.

8.12 Storage, Handling, and Accountability

All investigational supplies are to be kept in a secure area with controlled access.

Vials of Pevonedistat Injection for Solution for Infusion are to be stored at 2°C to 8°C.

Details of the storage and handling of azacitidine are provided in the VIDAZA USPI [10] or EU SmPC [11]. For instructions and precautions regarding preparation of docetaxel, carboplatin, and paclitaxel, refer to the applicable USPI/SmPC for each agent.

8.13 Other Protocol-Specified Materials

Refer to the Pharmacy Manual.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Council for Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the sponsor's project clinician for this study, the central laboratory and any additional clinical laboratories or vendors participating on the study may be found in the Study Manual(s). A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

9.3 Treatment Group Assignments

No randomization or stratification will be performed in this study. Patients will be assigned on the basis of their renal and hepatic function.

Laboratory value requirements per treatment arm for eGFR, total bilirubin, and ALT are provided in Table 9.a and Table 9.b for patients with hematologic malignancies and advanced solid tumors, respectively.

Table 9.a Laboratory Value Requirements per Treatment Arm for eGFR, Total Bilirubin, and ALT (Patients With Hematologic Malignancies Only)

Treatment Arm	eGFR (mL/min/1.73 m^2)	Total Bilirubin	ALT
Control	≥90	≤ULN	≤ULN
Renal	<30	≤ULN	≤2.5 × ULN
Mild hepatic	≥60	ULN <bilirubin ≤1.5 × ULN (not secondary to transfusions)	Any
Moderate hepatic	≥60	1.5 × ULN <bilirubin ≤3.0 × ULN (not secondary to transfusions)	Any

ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate; ULN: upper limit of the normal range.
Refer to Section 9.4.16 for information regarding hepatic and renal function laboratory result requirements.

Table 9.b Laboratory Value Requirements per Treatment Arm for eGFR, Total Bilirubin, and ALT (Patients With Advanced Solid Tumors Only)

Treatment Arm	eGFR (mL/min/1.73 m^2)	Total Bilirubin	ALT
Renal	<30	≤ULN	≤1.5 ×ULN [a] or ≤2.5 × ULN [b]
Mild hepatic [c]	≥60	ULN <bilirubin ≤1.5 × ULN	Any
Moderate hepatic [c]	≥60	1.5 × ULN <bilirubin ≤3.0 × ULN	Any

ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate; ULN: upper limit of the normal range.
Refer to Section 9.4.16 for information regarding hepatic and renal function laboratory result requirements.
[a] For patients who receive pevonedistat plus docetaxel only.
[b] For patients who receive pevonedistat plus carboplatin plus paclitaxel only.
[c] Patients with advanced solid tumors in the hepatic impairment arms will not receive combination treatment with pevonedistat and docetaxel.

Part A (all patients):

Patients in all arms will receive pevonedistat 20 mg/m^2 IV as a 1-hour infusion administered on Day 1.

Part B (patients with hematologic malignancies):

Starting in Cycle 1 of Part B, patients with hematologic malignancies and normal renal and hepatic function will receive 20 mg/m^2 pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine on Days 1 through 5, 8, and 9 in 28-day cycles.

As of Amendment 02, the Control Arm of the study completed enrollment. Patients with advanced solid tumors with normal renal and hepatic function will not be enrolled in the Control Arm.

Starting in Cycle 1 of Part B, patients with hematologic malignancies and severe renal impairment or mild or moderate hepatic impairment will receive pevonedistat on Days 1, 3, and 5 in combination with azacitidine (75 mg/m^2) on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles. Patients will receive azacitidine SC in Cycle 1. Azacitidine will be given SC or IV during Cycle 2 and beyond. The starting doses for pevonedistat and azacitidine in patients with organ impairment are described in Section 8.1.

Part B (patients with advanced solid tumors):

For patients with solid tumors, the investigator will assign each patient to pevonedistat plus docetaxel or to pevonedistat plus carboplatin plus paclitaxel based on his/her medical judgment, and per information provided in the package inserts for the SOC agents (docetaxel, paclitaxel, or carboplatin) for indications for use.

Starting in Cycle 1 of Part B, patients with advanced solid tumors and severe renal impairment or mild or moderate hepatic impairment will receive docetaxel or carboplatin plus paclitaxel in

combination with pevonedistat on Day 1, and pevonedistat alone on Days 3 and 5 in 21-day cycles.

The starting doses for pevonedistat, docetaxel, carboplatin, and paclitaxel in patients with advanced solid tumors are described in Section 8.1.

9.4 Study Procedures

Refer to the schedule of events (SOE) tables (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow and in the Study and Laboratory Manuals. When applicable, specific visit windows for study procedures are provided in the footnotes to the study schedule tables.

Nonessential protocol visits 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 coronavirus disease 2019 (COVID-19) pandemic. The reason for telemedicine (eg, COVID-19-related) and the assessments performed are to be captured in the electronic data capture (EDC).

9.4.1 Informed Consent

Each patient, or the patient's legally acceptable representative, must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's SOC.

Reconsent of Patients With Hematologic Malignancies Who Meet the Criteria for PD and Continue Study Treatment

Patients with HR MDS or HR CMML may be allowed to continue study treatment if they meet the criteria for PD based only on bone marrow blast count (without AML transformation) if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients with AML in this study may also be allowed to continue study treatment, even if they meet the criteria for PD based only on bone marrow blast counts if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who continue on study under these conditions must be reconsented before continuing study treatment.

9.4.2 Inclusion/Exclusion Confirmation

Confirmation of patient eligibility by the sponsor's project clinician (or designee) is required prior to enrollment. During screening, a patient eligibility checklist must be completed and submitted by the investigator for review and approval by the sponsor or designee before the patient is enrolled. Completion of the eligibility checklist is necessary to verify that the patient has met all of the inclusion and exclusion criteria. Source documentation allows for independent verification that patient eligibility has been determined by the proper methodology. Unless specifically requested,

additional source documentation does not need to be submitted with the checklist for the assessment of eligibility related to the other inclusion and exclusion criteria.

Refer to Section 9.4.16 for information regarding hepatic and renal function laboratory result requirements.

9.4.3 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

9.4.4 Medical History

During screening, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy. For patients with hematologic malignancies, see Section 7.1.2 for definitions relevant to medical history, including an assessment of bone marrow morphology (see Section 9.4.17.1 for additional details on bone marrow sample collection and evaluation). For patients with advanced solid tumors, see Section 7.1.3 for definitions relevant to medical history and Section 9.4.17.2 for details regarding evaluation of sites of disease by CT scan or MRI.

Information regarding any prior therapy for treatment of the patient's malignancy, including start and stop dates of each therapeutic agent and response to therapy, will be collected in the eCRF. In addition, all blood transfusions related to the patient's malignancy that the patient received within 8 weeks before enrollment will be recorded to document baseline transfusion dependence.

9.4.5 Physical Examination

A complete physical examination will be performed per SOC at screening and at the EOS/ET visit. A symptom-directed physical examination will be completed per SOC at the times specified in the SOE (Appendix A), and as clinically indicated at the discretion of the investigator.

9.4.6 Patient Height

Height will be measured only during screening.

9.4.7 Patient Weight

Weight will be measured during screening, within 3 days before Day 1 dosing in Part A, within 3 days before Day 1 dosing in all cycles in Part B, and at the EOS/ET visit. If the screening assessment was done within 3 days before Day 1 in Part A, an assessment at Day 1 in Part A will not be necessary.

The amount of study drug (pevonedistat and/or azacitidine, docetaxel, or paclitaxel, as applicable) to be administered will be based on BSA. BSA will be calculated using a standard formula (see example in Appendix H) on Day 1 in Part A and on Day 1 of each cycle in Part B if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

The amount of carboplatin to be administered will be based on exposure (AUC) (refer to Section 8.1.3 for details of carboplatin dose calculations).

9.4.8 ECOG PS

ECOG PS will be assessed at the times specified in the SOE (Appendix A). Refer to Appendix D for the PS grading scale.

9.4.9 Vital Signs

Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected as specified in the SOE (Appendix A) and as clinically indicated at the discretion of the investigator. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be completed before the collection of the blood sample, unless otherwise noted in the SOE (Appendix A).

9.4.10 Pregnancy Test

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

In Part B, 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. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

Women of childbearing potential are defined as any sexually active female subjects who meet the following criteria:

- Those who have not undergone hysterectomy or bilateral oophorectomy.
- Those who have not had natural menopause for 12 consecutive months or longer (ie, follicle-stimulating hormone [FSH] >40 IU/L and no menopausal period for at least 12 consecutive months; loss of menopausal periods following chemotherapy may not rule out childbearing potential).

9.4.11 Concomitant Medications and Procedures

All concomitant medications and procedures (excluding transfusions) will be recorded from the time of the first dose of any study drug through 30 days (+10 days) after the last dose of any study drug(s). RBC and platelet transfusions will be recorded from 8 weeks before enrollment through 30 days after the last dose of any study drug. See Section 8.4 and Section 8.5 for additional details regarding excluded and permitted concomitant medications and procedures.

9.4.12 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOE. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

9.4.13 Enrollment

Enrollment is achieved when the first dose of any study drug has been administered.

Procedures for completion of the enrollment information are described in the interactive web response system and Study Manual(s).

9.4.14 ECG

A 12-lead ECG will be performed at screening, within 3 days of Day 1 of each cycle in Part B, and at the EOS/ET visit, as specified in the SOE (Appendix A).

9.4.15 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Clinical laboratory evaluations will be performed as outlined in the following sections.

9.4.15.1 Clinical Chemistry, Hematology, and Urinalysis

As specified in the SOE (Appendix A), the following samples will be obtained: blood samples for analysis of hematology and clinical chemistry parameters shown in Table 9.c, Table 9.d, Table 9.e, and for coagulation parameters in Table 9.f; and urine samples for analysis of the parameters shown in Table 9.g. Assessments may be performed more frequently if clinically indicated at the discretion of the investigator.

Table 9.c Hematology Tests

Hematology
Hematocrit
Hemoglobin
Leukocytes with differential, including percent circulating blasts
Neutrophils (ANC); ANC will be calculated from the leukocyte count with differential count; see Appendix I
Platelet (count)

ANC: absolute neutrophil count.

Table 9.d Complete Serum Chemistry Panel

Complete Serum Chemistry Panel	
Albumin	Creatinine
ALP	Direct bilirubin
ALT	Glucose
AST	Magnesium
Bilirubin (total)	Phosphate
BUN	Potassium
Calcium	Sodium
CO_2	Urate
Chloride	

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CO_2: carbon dioxide.

Table 9.e Select Serum Chemistry Panel

Select Serum Chemistry Panel	
ALP	Bilirubin (total)
ALT	BUN
AST	Creatinine

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen.

Table 9.f Coagulation Panel

Coagulation Panel
PT
INR
aPTT

aPTT: activated partial thromboplastin time; INR: international normalized ratio; PT: prothrombin time.

Table 9.g Urinalysis With Microscopic Analysis

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Microscopic assessment of leukocytes, erythrocytes, bacteria, casts, and crystals
Occult blood	

The following Modification of Diet 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).

9.4.16 Assessment of Hepatic and Renal Function for Treatment Group Assignment

Patients will be assigned to treatment arms on the basis of their renal and hepatic function.

For assessment of hepatic function (total bilirubin and ALT), 2 blood samples will be required before the start of pevonedistat dosing on Day 1 of Part A. 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 in Part A, 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). 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.

9.4.17 Disease Assessment

9.4.17.1 Patients With Hematologic Malignancies

Disease assessments will be determined at time points indicated in the SOE based on local bone marrow aspirate blast counts and transfusions and laboratory data. The investigator's assessment of disease status will be entered into the eCRF for each time point.

9.4.17.1.1 Bone Marrow Aspiration and Bone Marrow Biopsy

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 prior to 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.

9.4.17.1.2 Assessment of Disease Response

Assessment of disease response will be conducted only in Part B of the study. Response criteria are provided in Appendix J. To determine disease response to pevonedistat treatment, the following procedures will be done (see Table C in Appendix A): bone marrow aspiration to assess disease response at Cycle 2 on Day 22 (+6 days) and then every third cycle afterward at any time between Day 15 and Day 28 until Cycle 11, provided that the disease assessment is available before Day 1 of the following cycle. After completion of Cycle 11, bone marrow aspiration will be performed after completion of every sixth cycle (or otherwise as clinically indicated at the discretion of the investigator) after the patient's previous scan at any time between Day 15 and Day 28, provided that the disease assessment is available before Day 1 of the following cycle.

Bone marrow samples will be analyzed locally at the clinical site to:

- Determine blast count on aspirate samples: Samples will be evaluated locally for blast count per institutional standard practice to inform disease burden assessment.
- Analyze cytogenetics for IPSS-R score determination and disease response assessment for patients with HR MDS and CMML. Chromosomal abnormalities and translocations that are routinely assessed for the diagnosis of MDS and AML are included in the IPSS-R.

Additional bone marrow aspiration(s) may be done if warranted by changes in peripheral blood counts, or otherwise as clinically indicated at the discretion of the investigator.

9.4.17.2 Patients with Advanced Solid Tumors

CT scans with IV contrast (unless medically contraindicated) or MRI of the chest, abdomen, and pelvis will be performed as entry criteria. 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.

CT scans with IV contrast encompassing the known sites of disease will also be performed during the study as specified in the SOE (Appendix A). A scan should be taken at the EOS visit if a scan has not been completed within 28 days prior to the EOS visit.

If a CT scan does not provide adequate imaging, MRI may be used to evaluate sites of disease. For each site of disease, the imaging modality (CT scan or MRI) used at entry must be used throughout the study. Tumor response will be assessed by the investigator at these times using the RECIST guidelines (version 1.1) as provided in Appendix J.

9.4.18 Biomarker, Pharmacodynamic, and PK Samples

9.4.18.1 Primary Specimen Collection

The primary specimen collection is displayed in Table 9.h.

Table 9.h Primary Specimen Collection

Specimen Name in Procedure in SOE (Appendix A)	Primary Specimen	Description of Intended Use	Sample Collection
Plasma samples for pevonedistat protein binding [a]	Plasma	Unbound pevonedistat PK parameters	Mandatory
Plasma samples for pevonedistat PK	Plasma	PK measurements	Mandatory
Plasma samples for azacitidine PK	Plasma	PK measurements	Mandatory
Urine samples for pevonedistat PK	Urine	PK measurements	Mandatory
Urine samples for azacitidine PK	Urine	PK measurements	Mandatory

PK: pharmacokinetic(s); SOE: schedule of events.

[a] 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.

9.4.19 PK Measurements

9.4.19.1 Blood Sampling

Blood samples for the determination of plasma concentrations of pevonedistat will be collected from all patients during Part A and Part B (Cycle 1) of the study at the timepoints specified in Appendix A, Table A, Table B, and Table D. Blood samples for the determination of plasma concentrations of azacitidine will be collected from patients with hematologic malignancies during Part B (Cycle 1) at the timepoints specified in Appendix A, Table B. The timing, but not the number, of PK blood samples may be changed if emerging data indicate that an alteration in the sampling scheme is needed to better characterize the PK of pevonedistat or azacitidine.

The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, with particular care given to the recording of blood sampling times for pevonedistat that occur close to the infusion.

To ensure that the measurements are representative of plasma exposure for pevonedistat, blood draws will be conducted in the arm opposite a patient's IV infusion. In the case that only a single arm is available, blood may be drawn as distal to the site for IV infusion as feasible, and the site of blood draw should be documented.

Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

If deemed appropriate, the blood samples collected in this study may be additionally analyzed to determine the plasma concentrations of pevonedistat major metabolites in humans.

The primary objective of PK sampling in this study is to measure pevonedistat concentrations in plasma. In addition, the end of infusion sample on Day 1 of Part A will be used for protein binding measurement to calculate unbound exposure of pevonedistat based on the measured total plasma concentrations and f_u. If the end of pevonedistat infusion sample during Part A is not bioanalytically feasible for protein binding measurement, the predose sample taken on Day 1 of Part A, spiked with pevonedistat concentrations, will be used for pevonedistat plasma protein binding. These PK samples may also be used for the exploratory measurement of plasma concentrations of metabolites of pevonedistat, if technically feasible and considered necessary for further understanding the metabolism of pevonedistat in patients with cancer.

9.4.19.2 Urine Sampling

Urine output will be collected from all patients during Part B (Cycle 1) of the study at the timepoints specified in Appendix A, Table B. Urine samples will be analyzed for estimate of urine PK parameters of pevonedistat and (in patients with hematologic malignancies) azacitidine. The exact date and time of each sample collection, and the volume of urine collected, should be recorded accurately.

Detailed instructions on the procedure for collection, processing, storage, and shipment of the urine samples will be provided in the Study Manual.

9.4.20 Pharmacodynamic Measurements

Not applicable to this study.

9.4.21 DNA Measurements

Not applicable to this study.

9.4.22 Banked Tumor Specimen Measurements

Not applicable to this study.

9.5 Completion of Study Treatment (for Individual Patients)

Part A:

Patients will be considered to have completed the protocol-specified treatment in Part A if they receive the single dose of pevonedistat.

Patients who have completed treatment in Part A and do not opt to continue into Part B will be considered to have completed study treatment.

Part B:

Patients who continue to Part B will be considered to have completed study treatment if they complete at least 12 cycles of treatment, discontinue treatment due to PD, or discontinue for any reason.

9.6 Completion of Study (for Individual Patients)

Part A:

Patients will be considered to have completed the study if they receive the Part A single dose of pevonedistat, provide samples for PK measurements (that will be used to provide data necessary for assessment of the effects of severe renal impairment or mild or moderate hepatic impairment on pevonedistat PK), and complete the EOS visit. Note an EOS visit is needed in Part A only if the patient does not continue into Part B for any reason (see SOE for Part A in Appendix A).

Part B:

Patients who opt to continue into Part B will be considered to have completed the study if they have completed study treatment and the EOS visit or until the sponsor terminates the study.

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Patients who do not complete the protocol-specified dosing, PK, and safety assessment in Part A may be considered nonevaluable and replaced.

Treatment with study drug may be discontinued for any of the following reasons:

- AE (see Section 10.1.2).
- Protocol deviation.
- PD.

  Note: Patients with hematologic malignancies may be allowed to continue study treatment if they meet the criteria for PD on the basis of only bone marrow blast count (without AML transformation in patients with HR MDS or HR CMML) if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment.

- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant.
- Pregnancy (patient must be discontinued).
- Study terminated by sponsor.
- Withdrawal by the patient.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOS visit will be completed as specified in the SOE. The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who have achieved objective clinical benefit from combination therapy (chemotherapy plus pevonedistat) and who have developed intolerance that is reasonably attributable to the chemotherapy after 2 or more cycles may continue on single-agent pevonedistat at the same dose and schedule upon request by the investigator and agreement with the sponsor. The dose of single-agent pevonedistat may be escalated to the maximum dose specified for the patient's treatment arm, as described in Section 8.1.

Patients who are eligible may be able to continue to receive study drug; see Section 6.3.5 for PTA.

9.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient.
- Completed study.
- Death.
- Other.
- PD.
- Initiation of hematopoietic stem cell transplant.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A PTE is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in persistent or significant disability or incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when,

based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 [1]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a WBC count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs and serious PTEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial *or* before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious PTEs, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 [1]. The criteria are provided in the Study Manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the start of study drug administration through 30 days (+10 days) after administration of the last dose of study drug and recorded in the eCRFs. 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 as follows:
  - Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.
  - Related and unrelated treatment-emergent SAEs and serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of the ICF in Part A through 30 days (+10 days) after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses provided below.

Call Center	Phone Number	Email	Fax
Dohmen Life Science Services	1-844-662-8532 Non–toll-free number: 1-510-740-1273	GlobalOncologyMedinfo @takeda.com	1-800-881-6092

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

Sponsor Safety Assessment

Safety data will be reviewed and assessed periodically by a global pharmacovigilance team and a cross-functional safety management team throughout the conduct of the study. These

cross-functional reviews will include a global safety lead from the study team, and other representation from other departments at Takeda such as Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, and Clinical Operations.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization (CRO) partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify such items as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the

audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

Analyses will be primarily descriptive in nature. No formal statistical hypothesis testing will be performed. A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

Summary tabulations will be presented to display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables along with the number and percentage (calculated using nonmissing values) per category for categorical data, unless specified otherwise.

13.1.1 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: patients who receive at least 1 dose of study drug, have a baseline disease assessment, and have at least 1 postbaseline disease assessment will be used for analyses of response.

13.1.2 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized in a descriptive fashion, including sex, age, race, ethnicity, weight, height, BSA, organ function category (ie, normal, severe renal impairment, or mild or moderate hepatic impairment), baseline disease characteristics, and other parameters as appropriate.

13.1.3 Efficacy Analysis

Efficacy measures will include disease response and duration of disease response. Analysis of all efficacy measures will be descriptive. Disease response in AML will be based on the ORR (CR + 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].

For AML patients, all CR includes both CR and CRi.

Disease response in patients with MDS or CMML 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) [6].

Disease response to pevonedistat in combination with docetaxel or carboplatin plus paclitaxel will be based on the best overall response as determined by the investigator using RECIST version 1.1 guidelines (Appendix J).

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 PD or death if no prior PD is documented. Responders without disease progression will be censored at the last clinical assessment of response.

13.1.4 PK 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 organ function group. 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 organ function group 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, and unbound values of C_{max}, AUC_{last}, AUC_{∞} and AUC_{τ}) by organ function and dose levels. Descriptive statistics will be presented for azacitidine PK parameters (C_{max}, T_{max}, AUC_{τ}, CL/F, $t_{1/2z}$, and CL_R by organ function and dose levels.

The analysis for the effects of organ impairment on pevonedistat PK will be based on unbound pevonedistat plasma exposure (AUC) following a single dose of pevonedistat in Part A. To assess the effects of severe renal impairment or mild or moderate 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), mild hepatic impairment (Mild Hepatic Arm) versus the normal group (Control Arm), and moderate hepatic impairment (Moderate 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, mild hepatic impairment vs normal, and moderate hepatic impairment vs normal) and corresponding 90% CIs for pevonedistat unbound AUC. The PK-evaluable population will be used for these analyses.

13.1.5 Pharmacodynamic Analysis

Not applicable.

13.1.6 PK/Pharmacodynamic Analysis

Not applicable.

13.1.7 Immunogenicity Analyses

Not applicable.

13.1.8 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 on the basis of the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory values using the safety population. Exposure to the study drugs and reasons for discontinuation will be tabulated.

A treatment-emergent adverse event (TEAE) in Part A is defined as any AE that occurs after administration of the single dose of study treatment 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 treatment in Part B and up through 30 days after the last dose of study drug in Part B.

AEs will be tabulated according to MedDRA by System Organ Class, High-Level Term, and Preferred Term 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).
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- SAEs.

- Drug-related SAEs.

A listing of TEAEs resulting in study drug discontinuation will be provided.

The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients) will be tabulated by System Organ Class and Preferred Term. Tabulation also will be provided that enumerates AEs by maximum intensity. Deaths, SAEs, and AEs resulting in study drug discontinuation will be tabulated.

Descriptive statistics for the actual values of clinical laboratory parameters (and change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Shift tables for laboratory parameters will be generated to show changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the pevonedistat safety profile.

Graphical displays will be used to show vital sign parameters over time separately for Part A and for Part B.

All concomitant medications collected from screening throughout the study period will be classified to Preferred Terms according to the WHO Drug Dictionary.

Additional safety analyses may be performed to enumerate rates of toxicities and to further define the safety profile of pevonedistat.

13.2 Interim Analysis

No interim analysis is planned.

13.3 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 nonevaluable may be replaced. The sample size of approximately 9 patients specified as being required for the PK-evaluable 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).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized) including, but not limited to, the investigator's binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches, such as remote source data verification (SDV) and remote source data review (SDR), may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local health authority and privacy laws and where permitted by the IRB/IEC.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected,

where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix C. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federalwide Assurance number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify the site of activation status once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives notification of activation status, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to the IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject, or the subject's legally acceptable representative, determines that he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization

(if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

Patients with PD based only on bone marrow blasts counts may be allowed to remain on study, after discussion between the investigator and project clinician or designee, if it is judged that they are deriving clinical benefit from doing so. Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, eg, subject name, address, and other identifier fields not collected on the subject's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study

information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov for the US and clinicaltrialsregister.eu for studies conducted in the EU, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

15.4.3.1 Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which

may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the clinical study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A SOE

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

Procedure	Screening [a] Days Window	PK Period Day 1	Day 2	Day 3	Day 4 [b]	EOS/ ET (+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					
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.					

Procedure	Screening [a] Days / Window	PK Period Day 1	Day 2	Day 3	Day 4 [b]	EOS/ ET (+10 days)
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); LVEF: left ventricular ejection fraction; 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). 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. LVEF must be <50% within 6 months prior to study enrollment. If a result within this time frame is unavailable, LVEF must be determined by echocardiography or multigated acquisition scan at screening.

[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) 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).

[k] Urinalysis will be analyzed locally. See Section 9.4.15.1. 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) postinfusion of pevonedistat	x [d]			
1 hour (± 15 minutes) postinfusion of pevonedistat	x [d]			
2 hours (±20 minutes) postinfusion of pevonedistat	x [d]			
3 hours (±20 minutes) postinfusion of pevonedistat	x [d]			
4 hours (±30 minutes) postinfusion of pevonedistat	x [d]			
6 hours (±30 minutes) postinfusion of pevonedistat	x [d]			
8 hours (±30 minutes) postinfusion 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 IV or SC administration	Days 1-7 or 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; COVID-19: coronavirus disease 2019; 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.

[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) 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. 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 (75 mg/m^2) on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles. Patients will receive azacitidine SC in Cycle 1. Azacitidine will be given SC or IV during Cycle 2 and beyond. 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 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 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) 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. 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. 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. See Section 8.0 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.

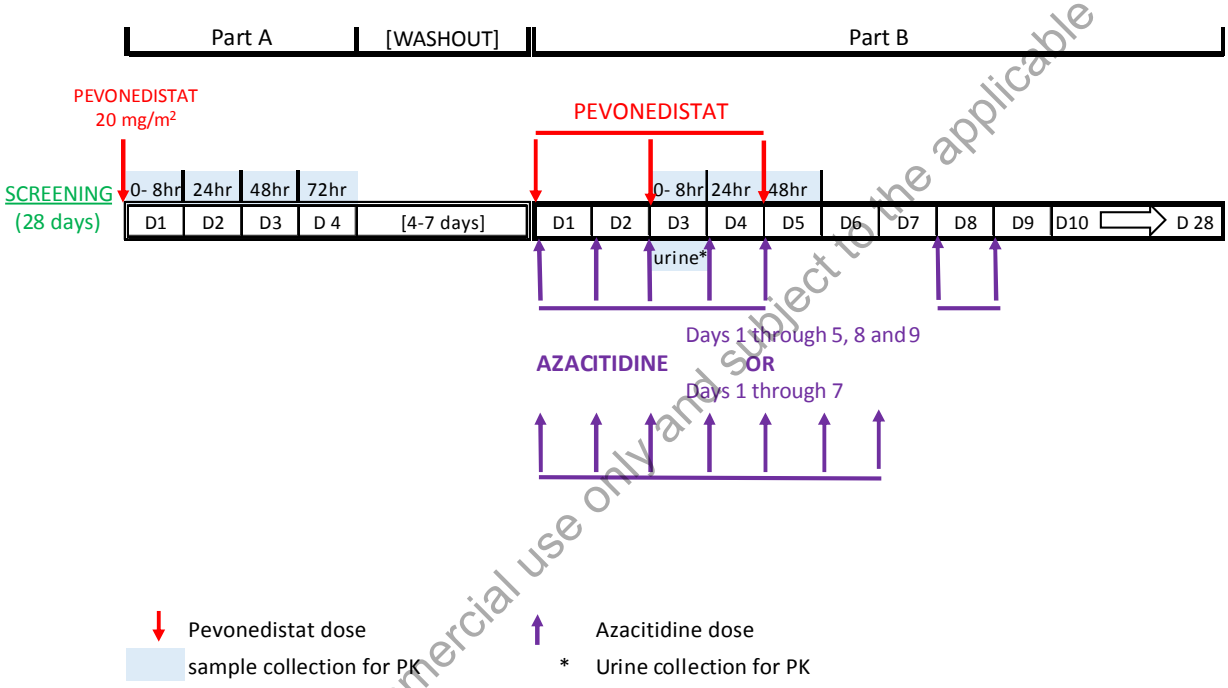
[b] The sample is to be collected at the end of pevonedistat infusion (immediately before stopping the IV infusion). The pevonedistat infusion takes approximately 1 hour.

[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 singe IV 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 75 mg/m2 azacitidine on Days 1-7 or Days 1–5, 8, and 9 in a 28 -day treatment period. Patients will receive azacitidine SC during Cycle 1 of Part B (PK assessment period). Azacitidine will be administered SC or IV during Cycle 2 and beyond. 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.

Appendix C Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix D ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken, 1982 [21].
ECOG: Eastern Cooperative Oncology Group.

Appendix E Definition of Postmenopausal

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Please refer to the following source for additional information: European Heads of Medicines Agencies Clinical Trial Facilitation Group; see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_ CTFG_Contraception.pdf.

Appendix F Acceptable Methods of Contraception Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered to be highly effective. Such methods include the following:

- Combined (estrogen and progestogen–containing) hormonal contraception associated with inhibition of ovulation [a]:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation [a]:
  - Oral.
  - Injectable.
  - Implantable. [b]
- Intrauterine device. [b]
- Intrauterine hormone-releasing system. [b]
- Bilateral tubal occlusion. [b]
- Vasectomized partner. [b,c]
- Sexual abstinence. [d]

Methods Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include the following:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide. [e]
- Cap, diaphragm, or sponge with spermicide. [e]

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
[b] Contraception methods that, in the context of this guidance, are considered to have low user dependency.
[c] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomized partner has received medical assessment of the surgical success.
[d] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.
[e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered an acceptable, but not a highly effective, birth control method.

Appendix G New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac disease [22].

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease

Appendix H BSA Calculation

BSA should be calculated using a standard formula. An example formula follows:

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

OR

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

Appendix I Formula for ANC Calculation

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

Example:

If total leukocyte count = 4.3×10^3/L; segmented neutrophils = 48%; band neutrophils = 2%

Then:

ANC = 4300 × (0.48 + 0.02) = 4300 × 0.5 = ANC of 2150

Appendix J Response Criteria for MDS, CMML, AML, and Solid Tumors

Response Criteria for Altering Natural History of MDS and CMML

Category	Response Criteria
CR	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines [a] Persistent dysplasia will be noted [a] Peripheral blood [b] Hgb ≥11 g/dL Platelets ≥100 × 10^9/L Neutrophils ≥1.0 × 10^9/L Blasts 0%
PR	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥50% over pretreatment but still >5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment Peripheral blood: any HI responses (see Table, below) will be noted separately, in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study
Failure	Death during treatment or PD (as defined below), or progression to AML or a more advanced MDS or CMML FAB/WHO subtype than pretreatment
Relapse after CR or PR	At least one of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Note: Transient cytopenias during chemotherapy courses should not be considered relapse, as long as they recover to the previous levels Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality

Category	Response Criteria
Progressive disease (PD)	Note: Transient cytopenias during chemotherapy courses should not be considered PD, as long as they recover to the previous levels; progression based on blood values should not be considered at all until after the post-Cycle 4 marrow draw If a patient has ≥50% increase in blast count from pretreatment (without AML transformation) but is still deriving benefit from this treatment (eg, improvement in peripheral blood counts), the patient may continue on study as agreed by the investigator and the sponsor's project clinician (or designee) For patients with: • Less than 5% blasts: ≥50% increase in blasts to >5% blasts. • 5%-9% blasts: ≥50% increase to >10% blasts. • 10%-19% blasts: ≥50% increase to >20% blasts. • 20%-30% blasts. Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets. • Reduction in Hgb by ≥2 g/dL. • New transfusion dependence.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

AML: acute myelogenous leukemia; CMML: chronic myelomonocytic leukemia; CR: complete response/remission; DFS: disease-free survival; FAB: French-American-British; Hgb: hemoglobin; HI: hematologic improvement; MDS: myelodysplastic syndromes; PFS: progression-free survival; PR: partial response/remission; WHO: World Health Organization.

[a] Dysplastic changes should consider the normal range of dysplastic changes.

[b] Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Response Criteria for HI for MDS and CMML

HI [a]	Response Criteria (Responses Must be At Least 8 Weeks in Duration)
Erythroid response (pretreatment, <11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.
Platelet response (pretreatment, $<100 \times 10^9$/L)	Absolute increase of $\geq 30 \times 10^9$/L for patients starting with $>20 \times 10^9$/L platelets Increase from $<20 \times 10^9$/L to $>20 \times 10^9$/L and by at least 100%
Neutrophil response (pretreatment, $<1.0 \times 10^9$/L)	At least 100% increase and an absolute increase $>0.5 \times 10^9$/L
Progression or relapse after HI [b]	At least one of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets. • Reduction in Hgb by ≥1.5 g/dL. • Transfusion dependence.

To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
CMML: chronic myelomonocytic leukemia; Hgb: hemoglobin; HI: hematologic improvement; MDS: myelodysplastic syndromes; RBC: red blood cell.

[a] Pretreatment counts will be the average of screening and Cycle 1 Day 1 predose samples.

[b] In the absence of another explanation, such as acute infection, a course of chemotherapy, gastrointestinal bleeding, hemolysis, and so forth. The 2 kinds of erythroid and platelet responses should be reported overall as well as by the individual response pattern.

Response Criteria for AML

Category	Response Criteria
Morphologic complete remission (CR)	A CR designation requires that the patient achieve the morphologic leukemia-free state and have an ANC of more than 1000/μL and platelets of ≥100,000/μL. A morphologic leukemia-free state requires less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. Hemoglobin concentration or hematocrit has no bearing on remission status, although the patient must be independent of transfusions. There should be no residual evidence of extramedullary leukemia.
Morphologic complete remission with incomplete blood count recovery (CRi)	After chemotherapy, some patients fulfill all of the criteria for CR except for residual neutropenia (<1000/μL) or thrombocytopenia (<100,000/μL).
Cytogenetic CR	Reversion to a normal karyotype at CR or CRi.
Partial remission (PR)	This designation requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. Thus, if the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pretreatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%. A repeat bone marrow aspiration after several weeks may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration. A value of ≤5% blasts may also be considered a PR if Auer rods are present.
Progressive disease (PD)	Because the IWG criteria for AML do not provide a standardized definition for PD [5], PD is defined in this protocol as one of the following: • >50% increase in bone marrow blasts from baseline value to >30% blasts. • >50% increase in circulating blasts from baseline value to >30% blasts in peripheral blood (in the exceptional case when bone marrow examination is not possible). • Development of biopsy-proven extramedullary disease, or new sites of extramedullary leukemia.
Relapse after CR	Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy). In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration.

AML: acute myelogenous leukemia; ANC: absolute neutrophil count; IWG: International Working Group.

Response Criteria for Target and Nontarget Lesions in Solid Tumors

Evaluation of Target Lesions	
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
Partial response	At least a 30% decrease from baseline in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.
SD	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
Evaluation of Nontarget Lesions	
CR	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
Non-CR/ Non-PD	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

Source: Eisenhauer, 2009 [23].
CR: complete response/remission; PD: progressive disease; SD: stable disease.

Overall Disease Response Criteria for Target and Nontarget Lesions in Solid Tumors

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	Partial response
CR	Not evaluated	No	Partial response
PR	Non-PD or not all evaluated	No	Partial response
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer, 2009 [23].
CR: complete response/remission; PD: progressive disease; SD: stable disease.

Appendix K Drugs Associated With Nephrotoxicity

The drugs listed in the table below are permitted to be used during the conduct of this study but should be used with caution.

Drugs Associated With Nephrotoxicity

Analgesics	**Cardiovascular agents**
Nonsteroidal anti-inflammatory drugs	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers
Antidepressants/mood stabilizers	Clopidogrel (Plavix), ticlopidine (Ticlid)
Lithium	**Contrast dye**
Antimicrobials	**Diuretics**
Acyclovir (Zovirax)	Loops, thiazides
Aminoglycosides	Triamterene (Dyrenium)
Amphotericin B (Fungizone; deoxycholic acid formulation more so than the lipid formulation)	**Herbals**
Beta lactams (penicillins, cephalosporins)	Chinese herbals with aristolochic acid
Foscarnet (Foscavir)	**Others**
Ganciclovir (Cytovene)	Allopurinol (Zyloprim)
Pentamidine (Pentam)	Gold therapy
Quinolones	Haloperidol (Haldol)
Rifampin (Rifadin)	Pamidronate (Aredia)
Sulfonamides	Phenytoin (Dilantin)
Vancomycin (Vancocin)	Quinine (Qualaquin)
Antiretrovirals	Zoledronate (Zometa)
Adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread)	
Indinavir (Crixivan)	
Calcineurin inhibitors	
Cyclosporine (Neoral)	
Tacrolimus (Prograf)	

Source: Modified from Naughton, 2008 [16].

Appendix L Hematologic Toxicity of Carboplatin Alone and in Combination With Paclitaxel

In 2 prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group, 789 chemotherapy-naïve patients with advanced ovarian cancer were treated with carboplatin or cisplatin in combination with cyclophosphamide every 28 days for 6 courses before surgical re-evaluation. See the table below for the hematologic adverse experiences of patients treated with carboplatin in combination with cyclophosphamide.

Hematologic Adverse Experiences of Patients With Ovarian Cancer Treated With Carboplatin in Combination With Cyclophosphamide

Adverse Experience	Laboratory Value	NCIC CTG Study % Patients (N=447)	SWOG Study % Patients (N=342)
Bone marrow			
Thrombocytopenia	<100,000/mm^3	70	59
	<50,000/mm^3	41	22
Neutropenia	<2000 cells/mm^3	97	95
	<1000 cells/mm^3	81	84
Leukopenia	<4000 cells/mm^3	98	97
	<2000 cells/mm^3	68	76
Anemia	<11 g/dL	91	88
	<8 g/dL	18	8
Infections		14	18
Bleeding		10	6
Transfusions		42	25

Source: Carboplatin US Package Insert 2011 [14].
NCIC CTG: National Cancer Institute of Canada Clinical Trials Group; SWOG: Southwest Oncology Group.

In a randomized clinical study, 798 patients with ovarian cancer were treated with either cisplatin plus paclitaxel or paclitaxel plus carboplatin therapy at 3-week intervals for 6 courses. See the table below for the hematologic adverse experiences of patients treated with paclitaxel/carboplatin.

Hematologic Toxicities and Associated Supportive Care in Patients With Advanced Ovarian Cancer Stratified by Treatment Arm and Toxicity Grade

		NCI CTC Grade, %												Difference [a] in the Proportions of Patients With Grades 3/4 Toxicity, %	
		Paclitaxel+Carboplatin Arm						Cisplatin+Paclitaxel Arm							
Toxicity	**Set**	**N**	**0**	**1**	**2**	**3**	**4**	**N**	**0**	**1**	**2**	**3**	**4**	**E**	**95% CI**
Hemoglobin	C	2209	29.1	49.4	20.1	1.3	0.1	2095	33.6	49.5	16.1	0.8	0.0	-0.6	-1.3 to 0.0
	P	388	9.0	40.7	44.3	5.4	0.5	382	14.7	44.2	37.2	3.9	0.0	-2.0	-5.1 to 1.1
Platelets	C	2193	71.9	19.9	5.2	2.5	0.5	2082	93.4	6.2	0.2	0.2	0.0	-2.9	-3.6 to -2.1
	P	388	43.3	31.2	12.6	10.1	2.8	382	78.3	19.4	1.3	1.0	0.0	-11.8	-15.3 to -8.4
Transfusions pRBCs [a]	C	1868	94.3	--	--	5.7	--	1766	97.2	--	--	2.8	--	-2.9	-4.2 to -1.6
	P	383	81.7	--	--	18.3	--	370	89.5	--	--	10.5	--	-7.7	-12.7 to -2.8
Leukocytes (WBC)	C	2200	37.0	22.6	29.3	10.8	0.3	2073	56.4	23.3	17.3	2.9	0.0	-8.1	-9.6 to -6.6
	P	388	13.4	16.0	38.7	30.4	1.5	382	31.4	35.1	32.7	10.5	0.3	-21.2	-26.8 to -15.6
Neutrophils	C	1842	56.9	12.9	12.8	12.4	5.0	1864	70.9	10.6	9.8	6.4	2.3	-8.7	-10.8 to -6.5
	P	371	31.3	12.9	18.9	21.6	15.4	373	48.0	13.1	16.9	15.0	7.0	-14.9	-21.4 to -8.5
Febrile neutropenia	C	2228	98.3	--	--	1.7	0.0	2110	99.3	--	--	0.7	0.0	-0.9	-1.6 to -0.3
	P	388	92.0	--	--	8.0	0.0	384	96.4	--	--	3.6	0.0	-4.3	-7.6 to -1.1
Supportive care: antibiotics [b]	C	1868	98.3	--	--	1.7	--	1768	97.9	--	--	2.1	--	0.4	-0.5 to 1.3
	P	383	93.2	--	--	6.8	--	370	90.5	--	--	9.5	--	2.7	-1.2 to 6.6
Supportive care: G-CSF [b]	C	1868	94.0	--	--	6.0	--	1767	98.2	--	--	1.8	--	-4.2	-5.5 to -3.0
	P	383	85.6	--	--	14.4	--	370	95.4	--	--	4.6	--	-9.8	-13.9 to -5.7

Source: du Bois, 2003 [24].

The symbol "--" denotes "not defined."

C: maximum grade over all courses; G-CSF: granulocyte colony stimulating factor; E: estimate; N: number of courses in set C and number of patients in set P; NCI CTC: National Cancer Institute Common Toxicity Criteria; P: maximum grade over all courses within a patient; pRBCs: packed red blood cells; WBC: white blood cell.

[a] Differences are calculated by subtracting the paclitaxel+carboplatin arm proportion from the cisplatin+paclitaxel arm proportion; statistically significant differences in proportions between the 2 treatment arms are in bold font. All percentages are rounded to 1 decimal place; therefore, the estimates may differ by ±1 from the difference of the percentages of the treatment arm columns.

[b] Transfusion of pRBCs and use of antibiotics and G-CSF were not assessed for the last treatment cycle within a patient. Use of antibiotics and use of G-CSF are graded in the same fashion as transfusion of pRBCs. Use of antibiotics/application of G-CSF is coded as a toxicity of Grade 3; a Grade 0 is applied otherwise.

Appendix M Excluded Strong CYP3A Inhibitors and Inducers

Use of strong CYP3A inhibitors and inducers listed in the table below should be avoided during pevonedistat therapy unless otherwise noted in the protocol.

In Vivo Inhibitors and Inducers of CYP3A

Strong Inhibitors	Strong Inducers
Clarithromycin	Carbamazepine
Idelalisib	Phenytoin
Itraconazole	Phenobarbital
Ketoconazole	Primidone
Nefazodone	Rifabutin
Posaconazole	Rifampin
Telithromycin	Rifapentine
Voriconazole	St. John's wort

CYP: cytochrome P450.
Strong CYP3A inhibitors and inducers should only be excluded during the Part A and Cycle 1 of Part B of the study where the pevonedistat pharmacokinetic measurements are conducted.
This is not an exhaustive list; refer to the following source:
https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Appendix N Protocol History

Amendment History:

Date	Amendment No.	Amendment Type	Region
27 May 2021	4	Substantial	Global
04 November 2020	3	Substantial	Global
29 June 2020	2	Substantial	Global
25 February 2019	1	Substantial	Global
07 November 2018	Initial protocol	Not applicable	Global

Rationale for Amendment 3

This document describes the changes in reference to the protocol incorporating Amendment 3 The primary reason for this amendment is to incorporate changes requested by global health authorities. In addition, this amendment permits alternative clinical site monitoring approaches, if needed, and where allowed by the local health authority, privacy laws, and permitted by the institutional review board/ethics committee (IRB/IEC). These changes to alternative monitoring procedures are intended to minimize the impact of the coronavirus disease-2019 (COVID-19) pandemic while ensuring data quality and integrity.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
1. Add use of strong cytochrome P450 (CYP)3A inducers within 14 days of baseline to the list of exclusion criteria. 2. Add strong CYP3A inducers and inhibitors to the list of excluded concomitant medications.	Although strong CYP3A inhibitors and inducers did not have clinically meaningful impact on pevonedistat systemic exposures based on results from Studies C15011 and Pevonedistat-1015, strong CYP3A inhibitors and inducers remain prohibited in this study in order to interpret the effects of organ impairment on pevonedistat PK without potential confounding factors. Change made in response to protocol review by global health authorities.	Section 2.0 STUDY SUMMARY Section 4.1.3.1 Clinical Pharmacokinetics Section 4.1.5 Potential for DDIs Section 7.2 Exclusion Criteria Section 8.4 Excluded Concomitant Medications and Procedures, including Table 8.f Concomitant Medications Excluded While Receiving Study Treatment: Combination Pevonedistat Plus SOC agents Appendix M Excluded Strong CYP3A Inhibitors and Inducers
3. Provide alternative clinical site monitoring approaches due to the COVID-19 pandemic.	To ensure data quality and integrity and maintain patient safety during the COVID-19 pandemic.	Section 14.1 Study Site Monitoring Visits Appendix A SOE Table B Footnotes

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
4. Revised the timeframe of contraception (and donation of eggs) in women of childbearing potential from 4 months to 6 months.	Change made in response to protocol review by global health authorities.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 7.2 Exclusion Criteria Section 8.6 Precautions and Restrictions
5. Added patients with previously untreated hematologic malignancies not suitable for induction therapy to inclusion criteria.	Clarified to make Inclusion Criteria section consistent with Overview of Study Design section.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria
6. Updated azacitidine dosing to permit subcutaneous (SC) or intravenous (IV) dosing during Cycle 2 and beyond in Part B. 7. Updated azacitidine dosing schedule to permit dosing on Days 1 through 7 or Days 1 through 5, 8, and 9 in 28-day cycles in Part B.	Clarified that azacitidine administration by SC and IV routes is permissible as per the United States Prescribing Information (USPI) and Summary of Product Characteristics (SmPC) and has been studied in Study C15009.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 8.1 Study Drug Administration Section 8.1.1 Instructions for Pevonedistat and Azacitidine Dosing Section 9.3 Treatment Group Assignments Appendix A SOE Table A Footnote l Appendix A SOE Table B Footnote a Appendix B Study Diagrams
8. Updated eligibility criterion to emphasize the role of patient's legally acceptable representative for voluntary written consent.	Clarified potential role of the patient's legally acceptable representative for consistency with existing language in Section 15.2 Subject Information, Informed Consent, and Subject Authorization.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria, #9 Section 9.4.1 Informed Consent
9. Updated protocol amendment history sections.	Change made to reflect the current format being used by the sponsor.	Section 1.3 Protocol Amendment 3 Summary of Changes Appendix N Protocol History

RATIONALE FOR AMENDMENT 2

The primary reasons for Amendment 2 were to include patients with moderate hepatic impairment in the study and to allow enrollment of patients with advanced solid tumors with severe renal impairment or mild or moderate hepatic impairment. These changes expanded participation in the organ impairment arms of the study without compromising the safety of the study participants or

the primary objectives of the study. For patients with solid tumors to be enrolled in this study, they must have had histologically or cytologically confirmed metastatic or locally advanced solid tumor(s), appropriate for treatment with one of the 2 combination therapies in Part B (docetaxel or carboplatin/paclitaxel), that had progressed despite standard therapy. Patients with solid tumors for whom conventional therapy was not considered effective were also eligible for enrollment. As patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with docetaxel [20], it was to only be administered to patients in the severe renal impairment arm.

Other modifications to the study design included removing the determination of the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of pevonedistat in combination with azacitidine in patients with organ impairment in Part A and adding assessment of the pharmacokinetics (PK) and safety of pevonedistat in combination with azacitidine in these specific patient populations in Part B. In addition, an evaluation of the safety of pevonedistat in combination with carboplatin plus paclitaxel in patients with mild or moderate hepatic impairment, or in combination with carboplatin plus paclitaxel or with docetaxel in patients with severe renal impairment, was to be performed in Part B of the study.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were included for clarification and administrative purposes only.

Changes in Amendment 2

1. Include patients with advanced solid tumors in the single-dose pevonedistat PK assessment in Part A and, if eligible, continue treatment with pevonedistat in combination with standard of care (SOC) chemotherapy (docetaxel or carboplatin plus paclitaxel) in Part B.
2. Include patients with moderate hepatic impairment in the assessment of pevonedistat PK in patients with organ impairment.
3. Remove dose escalation phase and determination of MTD/RP2D for pevonedistat in combination with azacitidine in patients with hematologic malignancies (myelodysplastic syndromes [MDS], chronic myelomonocytic leukemia [CMML], and acute myelogenous leukemia) from Part A.
4. Add secondary objectives to assess the PK of pevonedistat and azacitidine in combination treatment in patients with hematologic malignancies/organ impairment and to assess the PK of pevonedistat in patients with advanced solid tumors/organ impairment receiving combination treatment with SOC agents.
5. Revise starting dose, maximum dose, and intrapatient dose escalation rules for each of the organ impairment arms in the study.
6. Add dose modification guidelines for patients with advanced solid tumors treated with pevonedistat in combination with SOC agents.
7. Revise guidelines for pevonedistat dose adjustment based on serum transaminases, total bilirubin, and other toxicities.

8. Add guidance for management of cytopenia and infection for patients with hematologic malignancies and for use of granulocyte-colony stimulating factor in patients with advanced solid tumors.
9. Add inclusion and exclusion criteria for patients with advanced solid tumors.
10. Revise laboratory values required for enrollment to include patients with moderate hepatic impairment.
11. Add inclusion criterion to indicate that all patients should have an expected survival of at least 3 months from the date of enrollment in the study.
12. Clarify that medical history and diagnosis-related inclusion criteria for patients with hematologic malignancies must be met *at study entry*.
13. Add exclusion criterion for patients diagnosed or treated for a different malignancy within 2 years before enrollment or previously diagnosed with a different malignancy with any current evidence of residual disease (excluding prior MDS or CMML).
14. Add exclusion criterion for patients with end-stage renal disease requiring hemodialysis.
15. Add exclusion criterion for patients with Gilbert syndrome.
16. Remove use of strong cytochrome P450 (CYP)3A inducers within 14 days of baseline from list of exclusion criteria and remove strong CYP3A inducers and known breast cancer resistance protein inhibitors from the list of excluded concomitant medications.
17. Clarify and add exclusion criteria for patients with cardiovascular conditions.
18. Update the number of patients to be enrolled in the study and increase the number of study sites to approximately 25 to 30 sites.
19. Update vial volume and dilution instructions for pevonedistat to include a vial volume of 4.4 mL and a diluent of 0.9% saline solution.
20. Increase study duration to 3.5 years.
21. Clarify timing for collection of plasma samples for measuring pevonedistat protein binding.
22. Specify that adverse events 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).
23. Specify that nonessential protocol visits that do not require on-site sample collection and assessment may be completed via telemedicine.

RATIONALE FOR AMENDMENT 1

The primary reason for Amendment 1 was to remove eligibility criteria relevant to the absolute neutrophil count (ANC), platelets, and hemoglobin to be consistent with other studies in the pevonedistat program. Patients with hematologic malignancy (acute myeloid leukemia [AML] and myelodysplastic syndromes [MDS]) suffer from cytopenia and/or anemia related to their underlying illness, particularly in a relapse/refractory setting. The sponsor had also considered

feedback from the study investigators indicating that certain eligibility criteria may represent major hurdles for enrolling patients with underlying hematologic disease (AML and MDS) in urgent need of treatment. Therefore, changes were made to the original protocol to modify these restrictions without compromising patient safety and to make further clarifications regarding study execution. Sections relating to the definition of dose-limiting toxicities (DLTs) and dose modification guidelines were also revised to correlate with the aforementioned changes.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 1

1. Correct the study title to remove "relapsed/refractory" (also remove wording elsewhere in the protocol as appropriate to the study) and clarify study phase as 1/1b.
2. Delete requirements for ANC $\geq$1000/mm^3, platelet count $\geq$75,000/mm^3, and hemoglobin $\geq$8 g/dL from the inclusion criteria.
3. Delete Grade 4 neutropenia and Grade 4 thrombocytopenia from DLTs for hematologic toxicity.
4. Revise dose modifications.
5. Revise the table of Concomitant Medications and Procedures Permitted During the Study.
6. Clarify treatment group assignments by adding the laboratory value requirements per treatment arm.
7. Correct header in laboratory table by adding "Complete" to Serum Chemistry.
8. Correct header in laboratory table from "Select Serum Chemistry" to "Coagulation Panel."
9. Clarify the assessment of hepatic and renal function prior to enrollment.
10. Increase the number of study sites to support patient enrollment.
11. Update footnotes in Schedule of Events tables for clarification.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	01-Jun-2021 15:31 UTC
[redacted]	Clinical Pharmacology Approval	01-Jun-2021 16:23 UTC
[redacted]	Clinical Science Approval	01-Jun-2021 16:26 UTC
[redacted]	Biostatistics Approval	01-Jun-2021 16:43 UTC