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

NCT Number: NCT02782468

Protocol Approve Date: 23 June 2017

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

CLINICAL STUDY PROTOCOL PEVONEDISTAT-1012 AMENDMENT 03

Pevonedistat

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

Protocol Number:	Pevonedistat-1012
Indication:	Acute myeloid leukemia and myelodysplastic syndromes
Phase:	1/1b
Sponsor:	Millennium Pharmaceuticals, Inc.
Therapeutic Area:	Oncology

Protocol History

Original	24 February 2015
Amendment 01	30 October 2015
Amendment 02	04 February 2016
Amendment 03	23 June 2017

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Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

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Study Clinical Science Lead (or designee)	Signature	Date

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Program Statistician (or designee)	Signature	Date

[redacted]

Clinical Pharmacologist (or designee)	Signature	Date

Rationale for Amendment 03

This document describes the changes in reference to the protocol incorporating Amendment 03. The primary reason for this amendment is to adjust the contraception requirements for consistency with Clinical Trial Facilitation Group (CTFG) recommendations.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific examples of text changes, the rationale for each change, and where the changes are located, see Section 15.13.

Changes in Amendment 03

1. Adjust contraception requirements to be consistent with CTFG recommendations.
2. Clarify that when additional electrocardiograms will be performed immediately following pevonedistat administration, there is up to a 10-minute window for measurement.
3. Clarify that vital signs assessment includes a ±10-minute window.
4. Allow multiple-gated acquisition scans to also be used to assess left ventricular ejection fraction.
5. Clarify that the period of observation and collection for serious adverse events (SAEs) includes a +10-day window 30 days following the last administration of study drug.
6. Update the designation for the entity for SAE reporting.
7. [redacted].
8. Clarify that site-generated mutation reports are not required if not performed routinely per country/institutional guidelines.
9. Revise the test parameters for urinalysis with microscopic analysis for both study arms to include phosphate, and no longer include bilirubin and glucose.
10. Remove urine safety assessments from the clinical laboratory evaluations for both study arms.
11. Clarify that in the event of a dose delay, creatinine measurements can be delayed by up to 3 days.
12. Provide a definition of postmenopausal.
13. Clarify the minimum interval between doses of pevonedistat.
14. Remove the restriction on the timing of platelet transfusions and clarify the timing of transfusions for red blood cells, if necessary, to least 1 day prior to investigational product administration.

15. Clarify that lymphoblasts and myelocytes are included in hematology test measures.
16. Clarify the percentage increase of bone marrow and circulating blasts in the progressive disease definition.
17. Provide additional information on definition of relapse after clinical response.
18. Clarify that for acute myeloid leukemia patients, all complete remission includes both complete remission and complete remission with incomplete count recovery.
19. Update the investigator responsibilities for compliance with updated International Council for Harmonisation guidelines.
20. Allow the use of moderate and strong cytochrome P450 3A inhibitors during treatment Cycle 2 and beyond for all study arms.

PROTOCOL SUMMARY

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

Number of Patients: Approximately 37 patients will be enrolled in this study.

Study Objectives

Primary

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

Secondary

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

[redacted]

Overview of Study Design:

This is a multicenter, open-label, phase 1/1b dose escalation and expansion study of pevonedistat administered intravenously (IV) as a single agent and in combination with azacitidine in approximately 37 adult East Asian patients with World Health Organization defined AML or HR MDS. Patients will be administered a 60-minute IV infusion of pevonedistat with or without azacitidine (administered IV or subcutaneously).

The Single-Agent Arm will include East Asian patients with R/R AML or R/R MDS (including nonproliferative chronic myelomonocytic leukemia [CMML]) that meets the Revised International Prognostic Scoring System (IPSS-R) criteria for the very high, high, or intermediate risk group (higher risk [HR] MDS). Each 21-day treatment cycle includes treatment with pevonedistat (starting

dose of 25 mg/m^2) on Days 1, 3, and 5, followed by a rest period of 16 days.

Enrollment in the Combination Arm will only begin after the data from the first group of 3 patients in the Single-Agent Arm have been reviewed and the dose has been found to be safe and tolerable. The Combination Arm will include East Asian patients with AML (R/R or previously untreated disease) or MDS (R/R or previously untreated disease), including nonproliferative CMML, that meets the IPSS-R criteria for the very high, high, or intermediate risk group. In the pevonedistat+azacitidine Combination Arm, each 28-day treatment cycle includes the following: treatment with pevonedistat (starting dose of 10 mg/m^2) on Days 1, 3, and 5; treatment with azacitidine (75 mg/m^2) on Days 1 through 5, and 8 through 9; and a rest period of 19 days.

In both arms, serial blood samples for determination of PK parameters will be collected at prespecified time points during Cycle 1. [redacted]

A 3+3 schema will be used for dose escalation. The dose-escalation phase will evaluate the safety, tolerability, and PK of pevonedistat administered as a single agent or in combination with azacitidine. The dose level(s) determined to be safe during the dose-escalation phase of the study may then be expanded to as many as 12 patients in total to further confirm safety and investigate PK. At least 1 Japanese patient will be included in each group of 3 patients in the dose-escalation phase.

In the Single-Agent Arm, if a dose expansion group of up to 6 patients is added at the highest dose level, at least 1 additional Japanese patient will be included (unless at least 3 Japanese patients were enrolled at that dose level during dose escalation and emerging data support an adequate characterization of PK and safety, in which case no additional Japanese patients are needed in the expansion phase). In the Combination Arm, following dose escalation, an additional group of up to 6 patients will be added in the expansion phase for a total of up to 12 patients at the highest dose level. The total number of Japanese patients at the highest Combination Arm dose level will be at least 6.

Disease response assessments will be conducted using International Working Group (IWG) criteria for AML and modified IWG criteria for MDS (including CMML). Patients will continue in this study until disease progression or unacceptable toxicity occurs. No formal interim analysis is planned, but safety and PK data will be reviewed on an ongoing basis during the dose escalation and expansion phases of the study.

Study Population

Single-Agent Arm:

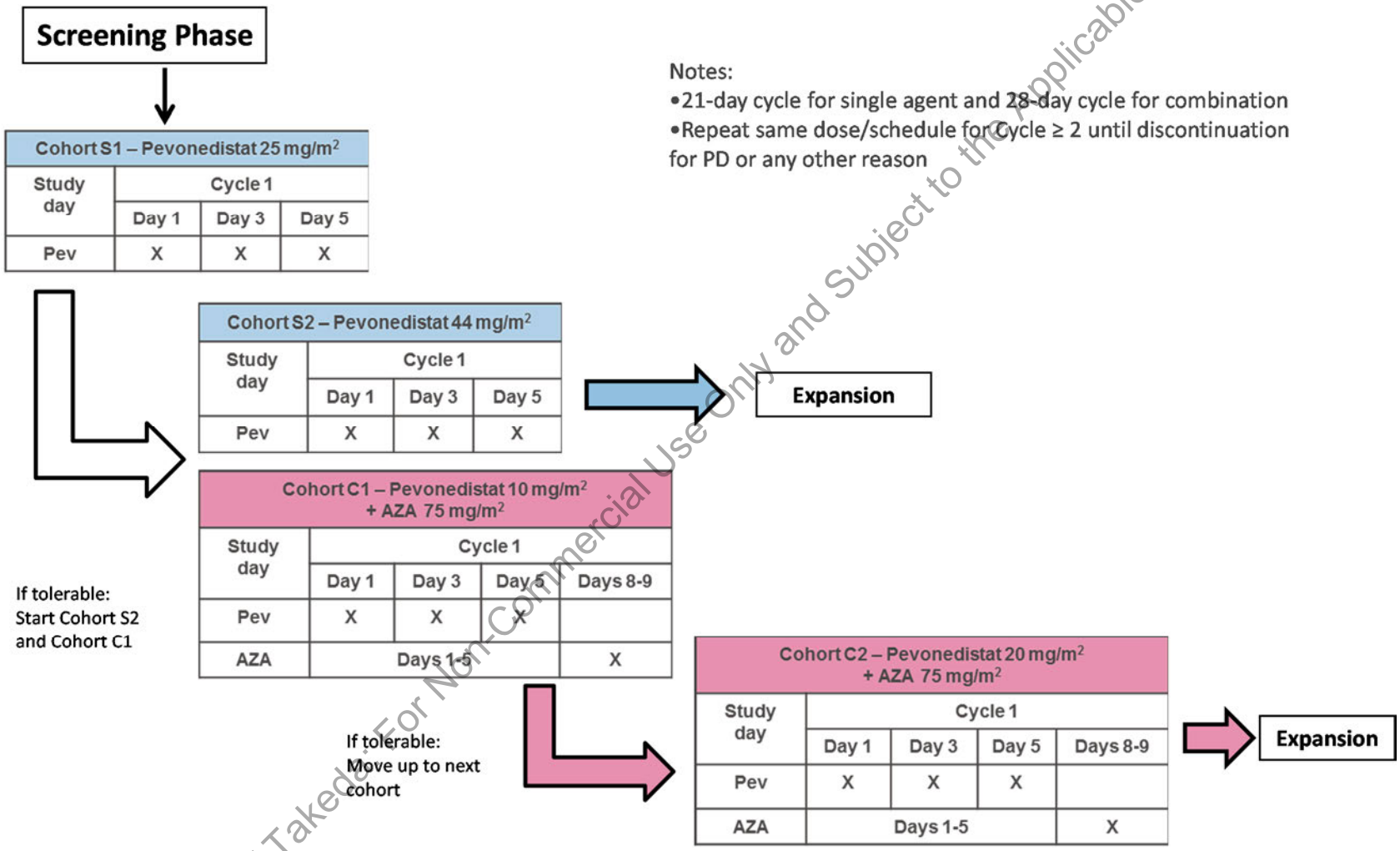
- Male and female East Asian patients with AML [1], including leukemia secondary to prior chemotherapy or resulting from an antecedent hematologic disorder, who have failed to achieve complete remission (CR) or who have relapsed after prior therapy (R/R) and are not candidates for potentially curative treatment.
- Male and female East Asian patients with MDS [2] that meets the IPSS-R criteria for the very high, high, or intermediate risk group [3], for whom standard curative, life-prolonging treatment does not exist or is no longer effective (R/R).
- Male and female East Asian patients with CMML-2 or CMML-1 that meets the IPSS-R criteria for the very high, high, or intermediate risk group [3], for whom standard curative, life-prolonging treatment does not exist or is no longer effective (R/R); patients with CMML-1 must have bone marrow blasts ≥5% [2].

Combination Arm:

- Male and female East Asian patients with AML [1], 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 (R/R) and are not candidates for potentially curative treatment. Patients are not to have been previously treated with azacitidine or decitabine.
- Male and female East Asian patients aged 60 years or older with previously untreated AML who have bone marrow blasts <30% and who are not candidates for standard induction chemotherapy. Patients are not to have been previously treated with azacitidine or decitabine.
- Male and female East Asian patients with MDS [2] that meets the IPSS-R criteria for the very high, high, or intermediate risk group [3], for whom standard curative, life-prolonging treatment does not exist or is no longer effective (R/R). Patients are not to have been previously treated with azacitidine or decitabine.
- Male and female East Asian patients with previously untreated MDS [2] that meets the IPSS-R criteria for the very high, high, or intermediate risk group [3]. Patients are not to have been previously treated with azacitidine or decitabine.
- Male and female East Asian patients with CMML-2 or CMML-1 that meets the IPSS-R criteria for the very high, high, or intermediate risk group [3]; patients with CMML-1 must have bone marrow blasts ≥5% [2]. Patients are not to have been previously treated with azacitidine or decitabine.

Duration of Study: The estimated total study duration includes 24 months of accrual plus the additional follow-up of 10 months after the last patient is enrolled.

STUDY OVERVIEW DIAGRAM



Abbreviations: AZA=azacitidine, C=combination, PD=progressive disease, Pev=pevonedistat, S=single-agent.

SCHEDULES OF EVENTS – SINGLE-AGENT ARM

Single-Agent Arm (Pevonedistat on Days 1, 3, and 5 of a 21-day Cycle) – Cycle 1

	Screening[a]	Treatment Cycle (21 Days)									EOS[b]
		Week 1							Weeks 2, 3		
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8 (±1 day)	Day 15 (±1 day)	
Study Drug Administration											
Pevonedistat infusion[c]		X			X	X					
Procedures											
Informed consent	X										
Inclusion/exclusion	X										
Demographics	X										
Complete medical history	X										
Physical examination including neurological exam	X										
Symptom-directed medical history and physical exam		X[d]							X	X	X
Height	X										
Weight	X	X[d]									
ECOG performance status	X	X[d]									X
Vital signs[e]	X	X	X	X	X	X			X	X	X
12-Lead ECG[f]	X	X	X		X	X					
Concomitant medications/ therapy[g]		Recorded from the first dose of pevonedistat through 30 days (+10 days) after the last dose of pevonedistat									
Hematology[h]	X	X[d]	X	X	X	X			X	X	X
Coagulation[i]	X										

Single-Agent Arm (Pevonedistat on Days 1, 3, and 5 of a 21-day Cycle) – Cycle 1

	Screening[a]	Treatment Cycle (21 Days)									EOS[b]
		Week 1							Weeks 2, 3		
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8 (±1 day)	Day 15 (±1 day)	
Full chemistry panel[j]	X	X[d]	X		X	X			X	X	X
Select chemistry panel[k]				X							
Urinalysis with microscopic analysis[l]	X	X[d]		X	X	X					
Echocardiogram[m]	X										
Serum pregnancy[n]	X	X[d]									
HBV and HCV screening[o]	X										
Serious pretreatment events and SAE collection[p]	Recorded from the time the informed consent is signed through 30 days (+10 days) after the last dose of pevonedistat. See Section 10.3 for additional information.										
AE collection		Recorded from the first dose of pevonedistat through 30 days (+10 days) after the last dose of pevonedistat									
Blood samples for PK[q] (see Serial Pharmacokinetic Sample Breakdown - Single-Agent Pevonedistat Arm)		X	X	X	X	X	X	X			
[redacted]											
Bone marrow collection:											
For disease monitoring, cytogenetics and karyotype[s,t]	X										X[u]
For molecular analysis[v]	X										
[redacted]											
Site generated mutation report[x]	X										

Single-Agent Arm (Pevonedistat on Days 1, 3, and 5 of a 21-day Cycle) – Cycle 1

	Screening[a]	Treatment Cycle (21 Days)									EOS[b]
		Week 1							Weeks 2, 3		
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8 (±1 day)	Day 15 (±1 day)	
[redacted]											

Abbreviations: AE=adverse event, CYP=cytochrome P450; DME=drug metabolizing enzymes, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOS=End of Study (visit), HBcAb= hepatitis B core antibody, HBsAb=hepatitis B surface antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HCVAb=hepatitis C virus antibody, [redacted], mRNA=messenger ribonucleic acid, PK=pharmacokinetics, SAE=serious adverse event, WBC=white blood cell.

Shading indicates dosing days.

a Within 28 days before the Cycle 1 Day 1 dose of pevonedistat.

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

c If required by local regulations or local clinical guidelines or preferred by the investigator, study drugs and protocol assessments may be administered in an in-patient setting during Cycle 1. For patients in Japan only, the full chemistry, hematology, and coagulation laboratory evaluations will be performed on the day the patient is discharged from the hospital.

d Except for measurement of WBC count, procedures conducted during the Screening period that are performed within 24 hours of Cycle 1 Day 1 can also be used as the Baseline 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.

e Vital sign measurements, including body temperature, diastolic and systolic blood pressure, and heart rate, will be obtained during Screening; on all dosing days (predose [before pevonedistat infusion] and 1 hour [±10 minutes] after the completion of pevonedistat infusion); on Days 2, 8, and 15; at EOS; and as clinically indicated. The Day 1 vital sign measurements will be taken pre-infusion and 30 minutes (±10 minutes), 1 hour (±10 minutes), 4 hours (±10 minutes), and 6 hours (±10 minutes) after the completion of pevonedistat infusion. At predose and 1 hour (±5 minutes) after completion of pevonedistat administration on Day 1, **orthostatic** blood pressure and heart rate measurements will be taken with the patient in a supine position and then standing, after waiting approximately 3 to 4 minutes. At all other time points, a sitting position is preferred for collection of vital signs. If a supine position is used, it should be used consistently for the same patient throughout the study. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection. 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 A 12-lead ECG will be performed during Screening; predose on Cycle 1 Day 1; and on Cycle 1 Days 1, 3, and 5, 6 hours (± 1 hour) after the completion of the pevonedistat infusion. An additional ECG will also be performed on Cycle 1 Day 1 immediately following pevonedistat administration (up to 10 minutes after the completion of pevonedistat infusion).

Single-Agent Arm (Pevonedistat on Days 1, 3, and 5 of a 21-day Cycle) – Cycle 1

		Treatment Cycle (21 Days)									
		Week 1							Weeks 2, 3		
	Screening[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8 (±1 day)	Day 15 (±1 day)	EOS[b]

g Use of moderate and strong CYP3A inhibitors are excluded for 7 days prior to first dose of study drug(s) and during treatment Cycle 1 only for both the Single-Agent Arm and the Combination Arm. For treatment Cycle 2 and beyond, the use of moderate and strong CYP3A inhibitors is permitted for both the Single-Agent Arm and the Combination Arm. See Section 6.5 for additional details.

h Hematology samples will be collected during Screening; predose on Days 1, 3, and 5; and at the Day 2, 8 (±1 day), Day 15 (±1 day), Day 21 (±1 day), and EOS visits. On Days 1, 3, and 5, samples can be drawn within 24 hours predose. **Please note: The sample for WBC count must be drawn before each dose on Days 1, 3, and 5 of Cycle 1. WBC count must be <50,000/µL before administration of pevonedistat; hydroxyurea may be used to control the level of WBC counts to no lower than 10,000/µL while on pevonedistat.** An additional sample will be taken on Cycle 1 Day 1 at 4 hours after the completion of the pevonedistat infusion.

i Coagulation panel at Screening includes prothrombin time (international normalized ratio) and activated partial thromboplastin time.

j Samples for the full clinical chemistry panel will be collected during Screening; Cycle 1 Days 1, 3, 5, 8 (±1 day), and 15 (±1 day) predose where applicable; and EOS. In addition, samples will be taken on Day 1 at 4 hours after infusion with pevonedistat.

k The select chemistry panel will include the following: blood urea nitrogen, creatinine, lactate dehydrogenase, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. The select chemistry panel will be collected on Day 2. In the event of a dose delay, creatinine measurements can be delayed up to 3 days.

l Urinalysis with microscopic analysis will include assessments of turbidity and color, pH, specific gravity, protein, phosphate, ketones, occult blood, nitrite, and leukocytes. These samples will be analyzed locally. See Section 7.4.11 for additional details.

m Echocardiogram or multiple-gated acquisition scan will be used to assess left ventricular ejection fraction.

n A serum pregnancy test will be performed for women of childbearing potential during Screening and predose Cycle 1. The results must be available and negative before the first dose of pevonedistat is administered.

o HBV and HCV screening may be conducted any time during the Screening period. HBV screening may include testing for HBsAg, HBsAb, HBcAb, or HBV viral load, as appropriate and per local institutional guidelines. HCV screening may include testing for anti-HCV antibody and viral load, as appropriate and per local institutional guidelines. Patients, who are HBsAg negative, and HBsAb and/or HBcAb positive, and/or HCVAb positive with negative viral load at screening will be monitored by assessment of viral load (HBV-DNA; HCV-RNA) as needed and based on local institutional guidelines.

p SAEs will be entered on the eCRF and also reported to BI Medical, Inc. Serious pretreatment events (occurring before the first dose of any study drug) will only be reported to BI Medical, Inc and will not be entered on the eCRF. SAEs 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).

q Blood samples (approximately 3 mL each) for determination of plasma concentrations of pevonedistat will be collected from all patients in the Single-Agent Arm during Cycle 1 at prespecified time points. A total of ~**54 mL** of blood will be drawn for PK analyses.

Single-Agent Arm (Pevonedistat on Days 1, 3, and 5 of a 21-day Cycle) – Cycle 1

	Screening[a]	Treatment Cycle (21 Days)									EOS[b]
		Week 1							Weeks 2, 3		
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8 (±1 day)	Day 15 (±1 day)	
r	[redacted]										

s A bone marrow biopsy (in addition to bone marrow aspirate) is required only at Screening to confirm the diagnosis; bone marrow aspirate will be collected at all other time points. 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. Historical results from up to 2 months prior to enrollment are acceptable for disease classification, but not disease status. If historical results do not show either t(15;17) or t(9;22), then these results can be used to ensure eligibility, provided a formal confirmatory report is sent as soon as it becomes available.

t Bone marrow aspirate will be collected at Screening (within 28 days before the first dose of study drug on Cycle 1 Day 1) for assessments of disease burden, [redacted] and karyotype, and at EOS for assessments of disease burden. [redacted]

u Only for patients who withdraw from the study for reasons other than disease progression.

v [redacted]

w [redacted]

x If mutation analysis is not performed routinely per country/institutional guidelines, it is not required.

Serial Pharmacokinetic Sample Breakdown - Single-Agent Pevonedistat Arm, Cycle 1

Time	Pharmacokinetic Sampling Schedule						
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Predose	X[a]				X[b]		
End of infusion[c]	X				X		
1 hour postinfusion[d] (±10 min)	X				X		
2 hours postinfusion[d] (±20 min)	X				X		
4 hours postinfusion[d] (±30 min)	X				X		
6 hours postinfusion[d] (±30 min)	X				X		
10 hours postinfusion[d] (±30 min)	X				X		
24 hours postdose (±1 hour)[e]		X				X	
48 hours postdose (±1 hour)[e]			X[b]				X

Abbreviation: IV=intravenous.

a The sample is to be collected within 1 hour before the start of pevonedistat infusion.

b The sample is to be collected within 10 minutes before the start of pevonedistat infusion.

c The sample is to be collected at the end of pevonedistat infusion (immediately before stopping the IV infusion).

d The time of sample collection is to be based on the time of **completion** of pevonedistat infusion on Day 1 (or Day 5).

e The time of sample collection is to be based on the time of **initiation** of pevonedistat infusion on Day 1 (or Day 5).

Single-Agent Arm (Pevonedistat on Days 1, 3, and 5 of a 21-day Cycle) – Cycle 2 and Beyond

	Treatment Cycle (21 Days)[a]							
	Week 1				Weeks 2, 3			
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	Day 8 (±1 day)	Day 15 (±1 day)	Day 21 (-6 days)	EOS[b]
Study Drug Administration								
Pevonedistat infusion	X		X	X				
Procedures								
Symptom-directed medical history and physical exam	X[c]				X	X		X
Weight	X[c]							
ECOG performance status	X[c]							X
Vital signs[d]	X	X	X	X	X	X		X
12-Lead ECG[e]	X							
Concomitant medications/therapy[f]	Recorded from the first dose of pevonedistat through 30 days (+10 days) after the last dose of pevonedistat							
Hematology[g]	X[c]		X	X	X	X		X
Full chemistry panel[h]	X[c]							X
Select chemistry panel[i]			X	X		X		
Blood phosphate				X				
Urinalysis with microscopic analysis[j]	X[c]							
SAE collection[k]	Recorded from the time the informed consent is signed through 30 days (+10 days) after the last dose of pevonedistat. See Section 10.3 for additional information.							
AE collection	Recorded from the first dose of pevonedistat through 30 days (+10 days) after the last dose of pevonedistat							
Bone marrow aspirate for disease monitoring[l]							X	X[m]

Abbreviations: AE=adverse event, CYP=cytochrome P450; ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOS=End of Study (visit), SAE=serious adverse event, WBC=white blood cell.

Shading indicates dosing days.

a For a new cycle of treatment with study drugs to begin, toxicities considered to be related to treatment with study drugs must have resolved to ≤Grade 1, to

the patient's Baseline values, or to a level considered acceptable by the investigator after discussion with the medical monitor (Section 6.4.1).

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

c If dosing falls on a Monday, the collection window may be extended to collect samples on a previous Friday.

d Vital sign measurements, including body temperature, diastolic and systolic blood pressure, and heart rate will be obtained during the following visits: Days 1, 3, and 5 (predose [before pevonedistat infusion] and 1 hour [±10 minutes]); Days 8 and 15; and EOS. A sitting position is preferred for collection of vital signs. If a supine position is used, it should be used consistently for the same patient throughout the study. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection. 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.

e On Day 1 of Cycle 2 and all subsequent treatment cycles, the 12-lead ECGs will be performed before any study drug dosing.

f Use of moderate and strong CYP3A inhibitors are excluded for 7 days prior to first dose of study drug(s) and during treatment Cycle 1 only for both the Single-Agent Arm and the Combination Arm. For treatment Cycle 2 and beyond, the use of moderate and strong CYP3A inhibitors is permitted for both the Single-Agent Arm and the Combination Arm. See Section 6.5 for additional details.

g Hematology samples will be collected predose on Days 1, 3, and 5; at the Day 8 (±1 day) and Day 15 (±1 day) visits; and at EOS. On Days 1, 3 and 5, samples may be drawn within 24 hours predose. **Please note: The sample for WBC count must be drawn before each dose on Days 1, 3, and 5 of each cycle. WBC count must be <50,000/µL before administration of pevonedistat; hydroxyurea may be used to control the level of WBC counts to no lower than 10,000/µL while on pevonedistat.**

h Samples for the full clinical chemistry panel will be collected on Day 1 (predose) of each cycle and at EOS.

i The select chemistry panel will include the following: blood urea nitrogen, creatinine, lactate dehydrogenase, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. The select chemistry panel will be collected predose (when applicable) on Days 3, 5, and 15 of each cycle. In the event of a dose delay, creatinine measurements can be delayed up to 3 days.

j Urinalysis with microscopic analysis will include assessments of turbidity and color, pH, specific gravity, protein, phosphate, ketones, occult blood, nitrite, and leukocytes. These samples will be analyzed locally. See Section 7.4.11 for additional details.

k SAEs will be entered on the eCRF and also reported to BI Medical, Inc. Serious pretreatment events (occurring before the first dose of any study drug) will only be reported to BI Medical, Inc and will not be entered on the eCRF. SAEs 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).

l Bone marrow aspirates will be collected to assess disease response at Cycle 2 and Cycle 4, within 6 days before the Day 21 visit, provided that the disease assessment is available before Day 1 of the following cycle. After Cycle 4, bone marrow assessments will be performed after completion of every third cycle (eg, Cycle 7, Cycle 10). Additional bone marrow aspirates may be performed if warranted by changes in peripheral blood counts.

m Only for patients who withdraw from the study for reasons other than disease progression.

SCHEDULES OF EVENTS – COMBINATION ARM

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8, and 9 of a 28-day Cycle) – Cycle 1

		Treatment Cycle (28 Days)											
		Week 1							Week 2		Week 3	Week 4	
	Screen-ing[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15 (±1 day)	Day 22 (±1 day)	EOS[b]
Study Drug Administration													
Pevonedistat infusion[c, d]		X			X	X							
Azacitidine administration[d, e]		X (Days 1 through 5, inclusive)							X	X			
Procedures													
Informed consent	X												
Inclusion/exclusion	X												
Demographics	X												
Complete medical history	X												
Physical examination including neurological exam	X												
Symptom-directed medical history and physical exam		X[f]							X		X	X	X
Height	X												
Weight	X	X[f]											
ECOG performance status	X	X[f]											X

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8, and 9 of a 28-day Cycle) – Cycle 1

	Screen-ing[a]	Treatment Cycle (28 Days)											EOS[b]
		Week 1							Week 2		Week 3	Week 4	
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15 (±1 day)	Day 22 (±1 day)	
Vital signs[g]	X	X	X	X	X	X			X	X	X		X
12-Lead ECG[h]	X	X	X		X	X							
Concomitant medications/therapy[i]		Recorded from the time of the first dose of any study drug through 30 days (+10 days) after the last dose of study drug(s)											
Hematology[j]	X	X[f]	X	X	X	X			X		X	X	X
Coagulation[k]	X												
Full chemistry panel[l]	X	X[f]	X		X	X			X		X	X	X
Select chemistry panel[m]				X									
Urinalysis with microscopic analysis[n]	X	X[f]		X	X	X							
Echocardiogram[o]	X												
Serum pregnancy[p]	X	X[f]											
HBV and HCV screening[q]	X												
Serious pretreatment events and SAE collection	Serious pretreatment events and SAEs will be recorded from the time the informed consent is signed through 30 days (+10 days) after the last dose of study drugs. See Section 10.3 for additional information.												
AE collection		Recorded from the first dose of any study drug through 30 days (+10 days) after the last dose of study drug(s)											
Blood samples for PK[s] (see Serial Pharmacokinetic Sample Breakdown - Pevonedistat+Azacitidine Combination Arm)		X	X	X	X	X	X	X					

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8, and 9 of a 28-day Cycle) – Cycle 1

	Screen-ing[a]	Treatment Cycle (28 Days)											EOS[b]
		Week 1							Week 2		Week 3	Week 4	
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15 (±1 day)	Day 22 (±1 day)	
[redacted]													
Bone marrow collection:													
For disease monitoring, cytogenetics, and karyotype[u,v]	X											X	X[w]
For molecular analysis[x]	X												
[redacted]													
Site-generated mutation report	X												
Site-generated cytogenetics report[z]	X												

Abbreviations: AE=adverse event, CYP=cytochrome P450; DME=drug metabolizing enzymes, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOS=End of Study (visit), HBcAb= hepatitis B core antibody, HBsAb=hepatitis B surface antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HCVAb=hepatitis C virus antibody, IV=intravenous(ly), miR=microRNA, mRNA=messenger ribonucleic acid, PK=pharmacokinetic, SAE=serious adverse event, WBC=white blood cell.

a Screening assessments will be performed within 28 days before the Cycle 1 Day 1 dose of study drugs.

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

c Patients will receive IV pevonedistat at a dose specified in Section 6.3. On Days 1, 3, and 5, when both study drugs are administered, azacitidine will be administered first, followed by pevonedistat. The infusion may be slowed or stopped and restarted for any associated infusion-related reactions. See

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8, and 9 of a 28-day Cycle) – Cycle 1

	Screen-ing[a]	Treatment Cycle (28 Days)											EOS[b]
		Week 1							Week 2		Week 3	Week 4	
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15 (±1 day)	Day 22 (±1 day)	

Section 6.1 for details of study drug administration.

d If required by local regulations or local clinical guidelines or preferred by the investigator, study drugs and protocol assessments may be administered in an in-patient setting during Cycle 1. For patients in Japan only, the full chemistry, hematology, and coagulation laboratory evaluations will be performed on the day the patient is discharged from the hospital.

e During Cycle 1, azacitidine 75 mg/m^2 will be administered IV on Days 1 through 5 (inclusive), 8, and 9. The dose of azacitidine may be reduced due to toxicities in accordance with Section 6.4.2.1 and Section 6.4.3.1. On Days 1, 3, and 5, when both drugs are administered, azacitidine will be administered first, followed by pevonedistat. Every effort should be made to administer study drug(s) around the same time of the day. See Section 6.1 for details of study drug administration.

f Except for measurement of WBC count, procedures conducted during the Screening period that are performed within 24 hours of Cycle 1 Day 1 can also be used as the Baseline 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.

g Vital sign measurements, including body temperature, diastolic and systolic blood pressure, and heart rate, will be obtained during Screening; on all dosing days (predose [before pevonedistat infusion] and 1 hour [±10 minutes] after the completion of pevonedistat infusion); Day 15; at EOS, and as clinically indicated. The Day 1 vital sign measurements will be taken before the azacitidine infusion, before the pevonedistat infusion, and 30 minutes, 1 hour, 4 hours, and 6 hours after the pevonedistat infusion. On dosing days when azacitidine is administered alone, an assessment of vital signs will be made predose and 1 hour (±10 minutes) postdose. On Days 3 and 5 (when both pevonedistat and azacitidine are administered), an assessment of vital signs will be made before the azacitidine dose, before the pevonedistat infusion, and 1 hour (±5 minutes) after completion of the pevonedistat infusion. At predose and 1 hour after completion of pevonedistat administration on Day 1, **orthostatic** blood pressure and heart rate measurements will be taken with the patient in a supine position and then standing, after waiting approximately 3 to 4 minutes. At all other time points, a sitting position is preferred for collection of vital signs. If a supine position is used, it should be used consistently for the same patient throughout the study. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection. 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 12-lead ECG will be performed during Screening and on Cycle 1 Day 1 predose (before azacitidine dosing), immediately after the infusion of pevonedistat is complete (up to10 minutes), and 6 hours (±1 hour) after the infusion of pevonedistat is complete. On Days 3 and 5, 12-lead ECGs will be performed before pevonedistat dosing as well as 30 minutes (±5 minutes) and 90 minutes (±5 minutes) after the start of pevonedistat infusion.

i Use of moderate and strong CYP3A inhibitors are excluded for 7 days prior to first dose of study drug(s) and during treatment Cycle 1 only for both the Single-Agent Arm and the Combination Arm. For treatment Cycle 2 and beyond, the use of moderate and strong CYP3A inhibitors is permitted for both the Single-Agent Arm and the Combination Arm. See Section 6.5 for additional details.

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8, and 9 of a 28-day Cycle) – Cycle 1

	Screening[a]	Treatment Cycle (28 Days)											EOS[b]
		Week 1							Week 2		Week 3	Week 4	
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15 (±1 day)	Day 22 (±1 day)	

j Hematology samples will be collected during Screening; before infusion with study drug(s) on Days 1, 2, 3, 5, and 8 (±1 day); Day 15 (±1 day); Day 22 (±1 day); and at the EOS visit. On Days 1, 3, and 5, samples can be drawn within 24 hours predose. **Please note: The sample for WBC count must be drawn before each dose on Days 1, 3, and 5 of Cycle 1. WBC count must be <50,000/µL before administration of pevonedistat; hydroxyurea may be used to control the level of WBC counts to no lower than 10,000/µL while on pevonedistat.** An additional sample will be taken on Cycle 1 Day 1 at 4 hours after the completion of pevonedistat infusion.

k Coagulation panel at Screening includes prothrombin time (international normalized ratio) and activated partial thromboplastin time.

l Samples for the full clinical chemistry panel will be collected during Screening; Cycle 1 Days 1, 3, 5, 8, (±1 day), 15 (±1 day), and 22 (±1 day) predose where applicable; and EOS. In addition, samples will be taken on Day 1 at 4 hours after infusion with pevonedistat.

m The select chemistry panel will be collected on Day 2 and will include the following: blood urea nitrogen, creatinine, lactate dehydrogenase, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. In the event of a dose delay, creatinine measurements can be delayed up to 3 days.

n Urinalysis with microscopic analysis will include assessments of turbidity and color, pH, specific gravity, protein, phosphate, ketones, occult blood, nitrite, and leukocytes. These samples will be analyzed locally. See Section 7.4.11 for additional details.

o Echocardiogram or multiple-gated acquisition scan will be used to assess left ventricular ejection fraction.

p A serum pregnancy test will be performed for women of childbearing potential during Screening and predose Cycle 1. The results must be available and negative before the first dose of pevonedistat is administered.

q HBV and HCV screening may be conducted any time during the Screening period. HBV screening may include testing for HBsAg, HBsAb, HBcAb, or HBV viral load, as appropriate and per local institutional guidelines. HCV screening may include testing for anti-HCV antibody and viral load, as appropriate and per local institutional guidelines. Patients, who are HBsAg negative, and HBsAb and/or HBcAb positive, and/or HCVAb positive with negative viral load at screening will be monitored by assessment of viral load (HBV-DNA; HCV-RNA) as needed and based on local institutional guidelines.

r SAEs will be entered on the eCRF and also reported to BI Medical, Inc. Serious pretreatment events (occurring before the first dose of any study drug) will only be reported to BI Medical, Inc and will not be entered on the eCRF. SAEs 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).

s Blood samples (approximately 3 mL each) for determination of plasma concentrations of pevonedistat will be collected from all patients in the Combination Arm during Cycle 1 at prespecified time points. A total of **~54 mL** of blood will be drawn for PK analyses.

t [redacted]

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8, and 9 of a 28-day Cycle) – Cycle 1

	Screening[a]	Treatment Cycle (28 Days)											EOS[b]
		Week 1							Week 2		Week 3	Week 4	
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15 (±1 day)	Day 22 (±1 day)	

u A bone marrow biopsy (in addition to bone marrow aspirate) is required only at Screening to confirm the diagnosis; bone marrow aspirate will be collected at all other time points. 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. Historical results from up to 2 months prior to enrollment are acceptable for disease classification, but not disease status.

v [redacted].

w Only for patients who withdraw from the study for reasons other than disease progression.

x [redacted]

y [redacted]

z If mutation analysis is not performed routinely per country/institutional guidelines, it is not required.

Serial Pharmacokinetic Sample Breakdown - Pevonedistat+Azacitidine Combination Arm, Cycle 1

Time	Pharmacokinetic Sampling Schedule						
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Predose	X [a]				X		
End of infusion[c]	X				X		
1 hour postinfusion[d] (±10 min)	X				X		
2 hours postinfusion[d] (±20 min)	X				X		
4 hours postinfusion[d] (±30 min)	X				X		
6 hours postinfusion[d] (±30 min)	X				X		
10 hours postinfusion[d] (±30 min)	X				X		
24 hours postdose (±1 hour)[e]		X[b]				X	
48 hours postdose (±1 hour)[e]			X[b]				X

Abbreviation: IV=intravenous.

a The sample is to be collected within 1 hour before the start of pevonedistat infusion and before azacitidine administration.

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

c The sample is to be collected at the end of pevonedistat infusion (immediately before stopping the IV infusion).

d The time of sample collection is to be based on the time of **completion** of pevonedistat infusion on Day 1 (or Day 5).

e The time of sample collection is to be based on the time of **initiation** of pevonedistat infusion on Day 1 (or Day 5).

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8 and 9 of a 28-day Cycle) – Cycle 2 and Beyond

	Treatment Cycle (28 Days)[a]								
	Week 1				Week 2		Week 3		
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	Day 8 (±1 day)[d]	Day 9 (±1 day)[d]	Day 15 (±1 day)	Day 24 (±4 days)	EOS[b]
Study Drug Administration									
Pevonedistat infusion[c]	X		X	X					
Azacitidine administration[d]	X (Days 1 through 5, inclusive)				X	X			
Procedures									
Symptom-directed medical history and physical exam	X[f]				X[e]		X		X
Weight	X[f]								
ECOG performance status	X[f]								X
Vital signs[g]	X	X	X	X	X	X			X
12-Lead ECG[h]	X								
Concomitant medications/ therapy[i]	Recorded from the time of the first dose of any study drug through 30 days (+10 days) after the last dose of study drug(s)								
Hematology[j]	X[f]		X	X	X		X		X
Full chemistry panel[k]	X[f]								X
Select chemistry panel[l]			X	X			X		
Blood phosphate				X					
Urinalysis with microscopic analysis[m]	X[f]								
Bone marrow aspirate for disease monitoring[n]								X	X[o]
Serious pretreatment events and SAE collection[p]	Recorded from the time the informed consent is signed through 30 days (+10 days) after the last dose of study drugs. See Section 10.3 for additional information.								

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8 and 9 of a 28-day Cycle) – Cycle 2 and Beyond

	Treatment Cycle (28 Days)[a]								
	Week 1				Week 2		Week 3		
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	Day 8 (±1 day)[d]	Day 9 (±1 day)[d]	Day 15 (±1 day)	Day 24 (±4 days)	EOS[b]
AE collection	Recorded from the first dose of any study drug through 30 days (+10 days) after the last dose of study drug(s)								

Abbreviations: AE=adverse event, CYP=cytochrome P450; ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOS=End of Study (visit), IV=intravenous(ly), SAE=serious adverse event; WBC=white blood cell.

a For a new cycle of treatment with study drugs to begin, toxicities considered to be related to treatment with study drugs must have resolved to ≤Grade 1, to the patient's Baseline values, or to a level considered acceptable by the investigator after discussion with the medical monitor (Section 6.4.1).

b The EOS visit will occur 30 days (+10 days) after the last dose of study drug(s) or before the start of subsequent antineoplastic therapy (other than hydroxyurea), if that occurs sooner.

c Patients will receive IV pevonedistat at a dose specified in Section 6.3. On Days 1, 3, and 5, when both study drugs are administered, azacitidine will be administered first, followed by pevonedistat. The infusion may be slowed or stopped and restarted for any associated infusion-related reactions. See Section 6.1 for details of study drug administration.

d Azacitidine 75 mg/m^2 may be administered IV or subcutaneously (per investigator's choice) on Days 1 through 5 (inclusive), 8, and 9 of each cycle. The dose of azacitidine may be reduced due to toxicities in accordance with Section 6.4.2.1 and Section 6.4.3.1. On Days 1, 3, and 5, when both drugs are administered, azacitidine will be administered first, followed by pevonedistat. Every effort should be made to administer study drug(s) around the same time of the day. See Section 6.1 for details of study drug administration.

e For patients who achieve complete remission, Day 8 physical examination is not necessary.

f If dosing falls on a Monday, the collection window may be extended to collect samples on a previous Friday.

g Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature, will be collected on all dosing days in all cycles, at EOS, and as clinically indicated. On dosing days when azacitidine is administered alone, an assessment of vital signs will be made predose and 1 hour (±5 minutes) postdose. On dosing days when both pevonedistat and azacitidine are administered, an assessment of vital signs will be made before the azacitidine infusion, before the pevonedistat infusion, and 1 hour (±5 minutes) after completion of the pevonedistat infusion. A sitting position is preferred for collection of vital signs. If a supine position is used, it should be used consistently for the same patient throughout the study. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection. 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 On Day 1 of Cycle 2 and all subsequent treatment cycles, the 12-lead electrocardiograms will be performed before any study drug infusion.

i Use of moderate and strong CYP3A inhibitors are excluded for 7 days prior to first dose of study drug(s) and during treatment Cycle 1 only for both the Single-Agent Arm and the Combination Arm. For treatment Cycle 2 and beyond, the use of moderate and strong CYP3A inhibitors is permitted for both

Combination Arm (Pevonedistat on Days 1, 3, and 5 in Combination With Azacitidine on Days 1 to 5, 8 and 9 of a 28-day Cycle) – Cycle 2 and Beyond

	Treatment Cycle (28 Days)[a]								
	Week 1				Week 2		Week 3		
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	Day 8 (±1 day)[d]	Day 9 (±1 day)[d]	Day 15 (±1 day)	Day 24 (±4 days)	EOS[b]

the Single-Agent Arm and the Combination Arm. See Section 6.5 for additional details.

j Hematology samples will be collected before infusion with study drug(s) during Cycle 2 on Days 1, 3, and 5; Day 8 (±1 day); Day 15 (±1 day); and at the EOS visit. On Days 1, 3, and 5, samples can be drawn within 24 hours predose. **Please note: The sample for WBC count must be drawn before each dose on Days 1, 3, and 5 of each cycle. WBC count must be <50,000/µL before administration of pevonedistat; hydroxyurea may be used to control the level of WBC counts to no lower than 10,000/µL while on pevonedistat.**

k Samples for the full clinical chemistry panel will be collected before infusion with study drugs on Day 1 and at the EOS visit. On Day 1, samples can be drawn within 24 hours predose. For Day 1 dosing only: if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

l The select chemistry panel will include the following: blood urea nitrogen, creatinine, lactate dehydrogenase, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. The select chemistry panel will be collected predose (when applicable) on Days 3, 5, and 15 of each cycle. On Days 3 and 5, samples can be drawn within 24 hours predose. In the event of a dose delay, creatinine measurements can be delayed up to 3 days.

m Urinalysis with microscopic analysis will include assessments of turbidity and color, pH, specific gravity, protein, phosphate, ketones, occult blood, nitrite, and leukocytes. These samples will be analyzed locally. See Section 7.4.11 for additional details.

n Bone marrow aspirates will be collected to assess disease response at Cycle 2 and Cycle 4, any time between Days 20 and 28, provided that the disease assessment is available before Day 1 of the following cycle. After Cycle 4, bone marrow assessments will be performed after completion of every third cycle (eg, Cycle 7, Cycle 10). Additional bone marrow aspirates may be performed if warranted by changes in peripheral blood counts.

o Only for patients who withdraw from the study for reasons other than disease progression.

p SAEs will be entered on the eCRF and also reported to BI Medical, Inc. SAEs 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). Serious pretreatment events (occurring before the first dose of any study drug) will only be reported to BI Medical, Inc and will not be entered on the eCRF.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from the time 0 to 24 hours
AUC_{∞}	area under the plasma concentration-time curve from 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from 0 to the last measurable concentration
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval
BCRP	breast cancer resistance protein
BSA	body surface area
BUN	blood urea nitrogen
CDL	cullin-dependent ubiquitin E3 ligase
Cdt-1	chromatin-licensing and DNA-replication factor-1
CL	clearance
C_{max}	single-dose maximum (peak) concentration
CMML	chronic myelomonocytic leukemia
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interactions
DLT	dose-limiting toxicity
DME	drug metabolizing enzyme
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Term
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
hERG	human ether-à-go-go related gene
HI	hematologic improvement
HIV	human immunodeficiency virus
HR	higher-risk
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
IV	intravenous(ly)
IWG	International Working Group
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
miR	microRNA
MLN4924	research name of pevonedistat hydrochloride; TAK-924
mRNA	messenger ribonucleic acid

Abbreviation	Term
MTD	maximum tolerated dose
NAE	NEDD8 activating enzyme
NCI	National Cancer Institute
NEDD8	neural precursor cell expressed developmentally down-regulated protein 8
NFE2	nuclear factor erythroid 2
Nrf2	NFE2-related factor 2
OATP	organic anion-transporting polypeptide
ORR	overall response rate
PD	progressive disease (disease progression)
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetic(s)
PR	partial remission
RBC	red blood cell
R/R	relapsed/refractory
SAE	serious adverse event
SC	subcutaneous
$t_{1/2}$	terminal disposition half-life
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia
Vss	volume of distribution at steady-state
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Diseases Under Treatment

1.1.1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a type of cancer that affects myeloid cells. AML encompasses a family of hematologic malignancies that can be categorized according to their cytogenetic and associated genetic abnormalities, which have major prognostic importance. For both Western and Asian populations, the majority of patients with AML are older than 60 years of age [4-6]; approximately 35% of patients with newly diagnosed AML are 75 years of age or older [7].

Treatment of AML requires initial induction chemotherapy with the goal of achieving complete remission (CR) with resolution of morphologically detectable disease and restoration of normal blood counts. This is followed by post-remission therapy to eradicate minimal residual disease. Both chemotherapy and allogeneic stem cell transplantation have been used, and each approach plays a significant role. Intensive combination chemotherapy usually includes cytarabine (also referred to as Ara-C) and anthracyclines with a CR rate between 45% and 60% (60% to 70% among younger patients) [8]. Stem cell transplantation has a greater antileukemia effect but is associated with a higher risk of treatment-related morbidity and mortality.

Although patients diagnosed with AML may initially experience relatively high CR rates, fewer than 25% of elderly AML patients live for 5 years, because most relapse with resistant disease [6,9]; cure of AML occurs only in a minority of patients with the available forms of chemotherapy [10].

1.1.1.2 Myelodysplastic Syndromes

Myelodysplastic Syndromes (MDS) are biologically and clinically heterogeneous hematopoietic disorders derived from an abnormal multipotent progenitor cell. Like AML, MDS occurs more frequently among the elderly; among Japanese patients, the median age at diagnosis is 76 years [11]. MDS can be classified as lower-risk or higher-risk (HR) based on life expectancy and the likelihood of progression to AML. Median survival for patients with MDS varies from years to months and decreases with increasing risk classification.

Because MDS are heterogeneous diseases, varied treatment options exist. Most patients with MDS are managed with non-curative treatment strategies to control symptoms, improve quality of life, improve overall survival, and decrease progression to AML. Treatment guidelines in Asia generally follow the National Comprehensive Cancer Network guidelines [12], and options vary based on an assessment of risk [3]. Although supportive care (eg, antibiotics as needed for infections, red blood cell [RBC] transfusions) may be the sole treatment for patients with lower-risk MDS, treatment for patients with higher-risk disease often includes hematopoietic growth factor therapy, immunosuppressive therapies, and deoxyribonucleic acid (DNA) hypomethylating agents (azacitidine and decitabine). Rarely, intensive chemotherapy is used in patients with HR MDS, but it generally results in significant toxicity and modest responses (uptodate.com/contents/treatment-of-high-or-very-high-risk-myelodysplastic-syndromes, Treatment of high or very high risk myelodysplastic syndromes, Accessed 08 December 2014) [13,14].

Hypomethylating agents produce objective hematologic responses in approximately half of MDS patients, including Asian patients [15,16], delay leukemic progression, improve quality of life, and–for azacitidine only–prolong survival in MDS patients. Nevertheless, treatment with hypomethylating agents is not curative, and most patients relapse within 2 years. Lenalidomide, an immunomodulatory thalidomide congener, significantly improves RBC transfusion-independence rates and increases hemoglobin, but it is approved only for use in patients with the 5q syndrome subtype of low-risk MDS [13,14].

The only known curative therapy for MDS is allogenic stem cell transplantation. However, only a minority of patients (typically with HR MDS) undergo this procedure due to contraindications and the limited availability of appropriate stem cell donors [17]. Even in these patients, treatment-related mortality and morbidity and high relapse rates compromise long-term disease-free survival (uptodate.com/contents/treatment-of-high-or-very-high-risk-myelodysplastic-syndromes, Treatment of high or very high risk myelodysplastic syndromes, Accessed 08 December 2014) [13,14].

1.1.2 Pevonedistat

Pevonedistat (MLN4924, TAK-924) is a first-in-class small molecule inhibitor of the NEDD8 (neural precursor cell expressed developmentally down-regulated protein 8)-activating enzyme (NAE) that is being developed for the treatment of malignancies.

NEDD8-activating enzyme is an E1 activating enzyme and is an essential component of the NEDD8 conjugation pathway, which controls the activity of a subset of ubiquitin E3 ligases, multiprotein complexes that transfer ubiquitin molecules to protein substrates that are then targeted to the proteasome for degradation. Cullin-dependent ubiquitin E3 ligases (CDLs) require conjugation to NEDD8 to be activated. Cullin-dependent ubiquitin E3 ligases control the timely ubiquitination and consequent proteasomal degradation of proteins with important roles in cell cycle progression and signal transduction, cellular processes that are integral to tumor cell growth, proliferation, and survival. Inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers by disrupting proteasomal degradation of a variety of critical regulatory proteins.

1.2 Nonclinical Experience

1.2.1 Single-Agent Pevonedistat

Pevonedistat treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines. Changes in protein levels observed in cultured cells treated with pevonedistat were consistent with the inhibition of NAE, in particular a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CDL substrates, including nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) and chromatin-licensing and DNA-replication factor-1 (Cdt-1). In most cell lines evaluated, NAE inhibition by pevonedistat led to DNA re-replication and accumulation of cells in the S phase of the cell cycle; this resulted in DNA damage and subsequent cell death through apoptosis [18-20].

Pevonedistat demonstrated pharmacodynamic and antitumor activity in solid tumor, lymphoma, and AML xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route. Results from testing a variety of AML nonclinical models in vitro and in vivo suggest that AML cells are particularly sensitive to pevonedistat (see the Investigator's Brochure [IB] for more details).

In vitro assay results indicated a low risk for human ether-à-go-go related gene (hERG) channel inhibition by pevonedistat or its 3 major circulating metabolites. In a Good Laboratory Practice (GLP)-compliant cardiovascular safety pharmacology assessment in male beagle dogs dosed via intravenous (IV) infusion at 15, 30, or 40 mg/kg (300, 600, or 800 mg/m^2, respectively), pevonedistat was not well tolerated at doses ≥30 mg/kg. Mortality and/or moribundity were observed within 24 hours postdose as a result of gastrointestinal injury at 40 mg/kg. In a separate GLP-compliant, 2-cycle, repeat-dose toxicology study in dogs, no test article-related effects were noted in the electrocardiogram (ECG) data.

The systemic toxicity of pevonedistat was assessed in GLP-compliant repeat-dose studies in rats and dogs. The dose-limiting toxicities (DLTs) in the 2-cycle studies for both species were gastrointestinal toxicity and bone marrow and lymphoid tissue depletion. Most adverse effects were resolving or had resolved after a 2-week recovery period. Pevonedistat did not result in lethality in either of the 5-cycle studies. The primary adverse test article-related effects in IV-dosed dogs included an acute phase response (increased body temperature, decreased albumin, increased globulin, increased monocytes and neutrophils, and increased fibrinogen levels); neutrophilic infiltrates in multiple tissues; and in males, vacuolation and degeneration of the seminiferous epithelium of the testes. Most adverse effects were reversing or had reversed after a 2-week recovery period in both rats and dogs. Given that there were prominent effects on testes and ovaries noted at all doses tested in the GLP-compliant repeat-dose toxicology studies in both dogs and rats, pevonedistat likely represents a substantial reproductive and developmental hazard.

Detailed information regarding the nonclinical pharmacology and toxicology of pevonedistat may be found in the IB.

1.2.2 Pevonedistat With Azacitidine

The combination of pevonedistat with azacitidine demonstrated synergistic or additive effects on viability of AML cell lines treated in vitro. Combination index analysis demonstrated synergy of pevonedistat with azacitidine in 2 AML cell lines (OCI-M2 and NB-4) and additivity in 2 additional AML cell lines (THP-1 and HL-60). The combination of pevonedistat and azacitidine in HL-60 and OCI-M2 cell lines resulted in increased DNA damage (measured by phospho-H2AX) and apoptosis (measured by cleaved caspase-3) compared to the levels of these markers induced by single-agent pevonedistat or azacitidine.

The benefit of the combination of pevonedistat with azacitidine was confirmed in vivo with immunocompromised mice bearing HL-60, OCI-M2, and THP-1 subcutaneous tumor xenografts. Pevonedistat in combination with azacitidine demonstrated additive or synergistic antitumor activity and tumor regression in all 3 subcutaneous xenograft models, which represent both azacitidine-sensitive (OCI-M2) and azacitidine-insensitive (HL-60 and THP-1) models. In OCI-M2, azacitidine and pevonedistat as single agents inhibited tumor growth, but the combination of these agents resulted in tumor regressions with a statistical assessment of synergy. In THP-1, although pevonedistat as a single agent inhibited tumor growth without causing regressions and azacitidine as a single agent had only a marginal effect on tumor growth, the combination caused regressions and delayed tumor regrowth

following the treatment period. In HL-60, tumor regressions were seen with the combination of pevonedistat and azacitidine at dose levels that had minimal or moderate antitumor activity as single agents. Furthermore, in a disseminated xenograft model in which HL-60 cells were inoculated into immunocompromised mice by IV injection, pevonedistat and azacitidine as single agents both extended survival time compared to a control group, but the combination extended survival time longer than would be expected from an additive combination, thereby demonstrating a synergistic effect on survival.

Detailed information regarding the nonclinical pharmacology and toxicology of pevonedistat may be found in the IB.

1.3 Clinical Experience

As of 22 January 2015, approximately 350 patients diagnosed with advanced malignancies including solid tumors, AML, melanoma, lymphoma, multiple myeloma, HR MDS, and acute lymphoblastic leukemia (ALL) have been enrolled in the overall clinical development program. Among these indications, pevonedistat has reported single-agent clinical activity in a phase 1 study (Study C15003) in relapsed/refractory (R/R) AML patients. In Study C15003, responses (complete remissions and partial remissions) were observed in a variety of patient settings, including postallogeneic transplant, therapy-related AML, and primary refractory AML [21]. In addition, a combination with azacitidine is currently being investigated in elderly patients with treatment-naïve AML; combination treatments in patients with solid tumors are also being investigated with docetaxel, gemcitabine, and a combination of carboplatin and paclitaxel.

Study C15009 is currently evaluating the combination of escalating doses of pevonedistat on Days 1, 3, and 5 with 75 mg/m^2 azacitidine administered (IV or SC) on a 5-on/2-off (weekend)/2-on schedule in 28-day cycles in treatment-naïve AML patients, aged ≥60 years, who are unlikely to benefit from standard induction therapy [22]. As of 22 January 2015, data are available for 42 patients enrolled in Study C15009 who received at least 1 dose of pevonedistat in combination with azacitidine; these patients had completed a total of approximately 170 cycles. In the dose escalation cohorts, 6 patients received 20 mg/m^2 pevonedistat, and 3 patients received 30 mg/m^2. The maximum tolerated dose (MTD) was determined to be 20 mg/m^2 pevonedistat given on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine given on Days 1 through 5, 8, and 9, in 28-day treatment cycles. The DLTs supporting this determination were elevations in LFTs (please refer to the IB for additional information regarding DLTs in Study C15009). The most common adverse events

(AEs), reported by ≥25% of patients, were constipation, febrile neutropenia, anemia, decreased appetite, thrombocytopenia, and fatigue. Additional preliminary safety information from Study C15009 is provided in Section 1.6.3. The nature and frequency of the reported toxicities (excluding DLTs) were similar to previous reports for azacitidine alone. Preliminary pharmacokinetic (PK) data showed that addition of azacitidine did not alter the known PK profile of single-agent pevonedistat.

In Study C15009, a total of 13 patients experienced partial remission or better; 5 patients had a best response of complete remission, and 8 patients had a best response of partial remission as of the data cutoff of 22 January 2015. Combination therapy with pevonedistat and azacitidine was generally well tolerated. The characteristics of the observed responses suggest an added benefit from the addition of pevonedistat compared with azacitidine alone.

1.4 Pharmacokinetics of Pevonedistat

1.4.1 Nonclinical PK and Risk Assessment for Drug-Drug Interactions

The absorption, distribution, metabolism, and excretion properties of pevonedistat have been studied in Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and chimpanzees. The whole blood clearance (CL) is low in all animal species, likely as a result of the extensive partitioning of pevonedistat into RBCs. The plasma terminal disposition half-life ($t_{1/2}$) varied from short (less than 1 hour in rats) to relatively long (15 hours in monkeys). The major elimination pathway of pevonedistat in animals is through the hepatic route. Urinary excretion of unchanged pevonedistat was negligible (<5%) in rats and primates. After an IV dose of [^{14}C] pevonedistat, radioactivity was primarily excreted in the feces in intact rats and in bile duct-cannulated rats; excretion was almost complete by 24 hours postdose. No plasma metabolite accounted for more than 10% of the total plasma radioactivity, suggesting potentially low systemic exposure to metabolites.

In vitro pevonedistat is metabolized via hydroxylation and oxidation, predominantly by cytochrome P450 (CYP) 3A4 with a small contribution from CYP2D6. Therefore, there is a potential for drug-drug interactions (DDIs) when pevonedistat is co-administered with drugs that are CYP3A inhibitors or inducers. A phase 1 DDI study (C15011) is currently evaluating the effects of CYP3A-mediated inhibition of pevonedistat in patients with solid tumors (see Section 1.6.4). Pevonedistat does not inhibit CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 and weakly and reversibly inhibits both CYP2B6 and 2C8; it does not induce CYP1A2, 2B6, and 3A4/5. On the basis of these in vitro data, pevonedistat is unlikely to affect the PK of drugs that are metabolized by these CYPs. In vitro, pevonedistat is a

substrate for the drug efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and is also a weak inhibitor of BCRP-mediated transport (concentration producing 50% inhibition [IC_{50}] of 6.3 μM). Additional transport studies with organic anion-transporting polypeptides (OATPs) in sandwich-cultured human hepatocytes showed that pevonedistat can inhibit the hepatic uptake of estrone-3-sulfate, simvastatin, and lovastatin (IC_{50} of 29.1 μM, 0.4-4.9 μM, and 0.9 μM, respectively). Inhibition of OATP-mediated uptake of simvastatin and lovastatin was observed in hepatocytes from some, but not all, donors. On the basis of these data, co-administration of pevonedistat with known P-gp or BCRP inhibitors is generally not permitted, whereas the potential exists, albeit low, for drug interactions with BCRP or OATP substrates.

Additional details on nonclinical PK information are provided in the IB.

1.4.2 Clinical PK

Clinical PK data are summarized in the IB. Single- and multiple-dose PK of pevonedistat have been evaluated in adult patients with solid tumors or hematologic malignancies. In these studies, pevonedistat was administered IV at dose levels of 25 to 278 mg/m^2 and with various daily or intermittent dosing schedules within 21-day treatment cycles. Plasma concentrations of pevonedistat declined in a multi-exponential manner at the end of a 1-hour IV infusion, with little or no notable drug accumulation upon repeat dosing as frequently as once a day. This observation is consistent with a mean terminal elimination half-life of approximately 10 hours (range, 7.7-15.2 hours) estimated across doses and schedules. Pevonedistat PK was linear over the dose range studied based on the area under the plasma concentration-time curve (AUC) from the time 0 to 24 hours (AUC_{24}) that increased proportionately with dose. Upon exploration of the effects of patient-specific covariates on pevonedistat population PK, body size and age influenced the clearance of pevonedistat, whereas only body size was important for all volume of distribution parameters. Additionally, data are available in 29 treatment-naïve, elderly AML patients who received IV pevonedistat at 20 mg/m^2 (n=26) and 30 mg/m^2 (n=3) on Days 1, 3, and 5 in combination with IV/SC azacitidine 75 mg/m^2 on a 5-on/2-off (weekend)/2-on schedule (Study C15009) [22]. These data indicate that pevonedistat PK remains unaffected by 5 continuous days of azacitidine dosing when compared to single-agent pevonedistat PK data from the earlier study in AML patients.

1.5 Study Rationale

This is an open-label, phase 1/1b dose escalation and expansion study of pevonedistat alone and in combination with 75 mg/m^2 azacitidine to be conducted in adult East Asian patients (eg, patients from countries including but not limited to Japan, Taiwan, and South Korea) with AML or HR MDS. The pevonedistat clinical program is intended to be expanded globally, and all the safety and PK information generated to date have come from patients in the United States (US). This study is intended to assess the safety, tolerability, and PK of pevonedistat alone and in combination with 75 mg/m^2 azacitidine, over a range of prespecified dose levels, in East Asian patients with hematologic malignancies, in order to support global clinical development.

1.5.1 Rationale for Dose and Schedule

Because this study will be the first clinical study of pevonedistat in East Asia, the safety, tolerability, and PK profiles of pevonedistat when given as a single agent will be evaluated first. Additionally, evaluation of the PK similarity of single-agent pevonedistat between Western and Asian populations can be used to support future evaluation of pevonedistat in combination with other standard-of-care agents in Asia. A total of 227 patients with solid tumors or hematologic malignancies from 4 phase 1 studies conducted in the US received pevonedistat via 1-hour IV infusion at doses ranging from 25 to 278 mg/m^2 on multiple schedules for up to 19 cycles. The majority of patients in these studies were White; although only 6 patients were Asian in the existing clinical database, no obvious differences in the kinetic behavior were noted. In 1 of these studies (Study C15003), pevonedistat was evaluated in 72 patients previously diagnosed with AML, MDS, or ALL, for whom standard curative, life-prolonging treatment did not exist or was no longer effective. Of these, 43 patients received pevonedistat on Days 1, 3, and 5 at the dose levels of 25 to 78 mg/m^2. Because no study drug-related deaths were reported, all but 1 of the study drug-related serious adverse events (SAEs) were laboratory abnormalities, and all of these events resolved and the patients recovered, the dose and schedule of 50 mg/m^2 pevonedistat on Days 1, 3, and 5 of a 21-day cycle was chosen as the recommended phase 2 dose for pevonedistat when given as a single agent.

In the ongoing Study C15009, which administers pevonedistat+azacitidine in patients 60 years of age and older with AML, 23 patients (79%) were DLT-evaluable. Two of these patients experienced a DLT at a pevonedistat dose of 30 mg/m^2: 1 patient developed Grade 2 increased bilirubin, and 1 patient developed Grade 3/4 increased transaminases without clinical sequelae. No patients experienced DLTs at a pevonedistat dose of 20 mg/m^2. Based

on these results, the MTD of the combination was determined to be 20 mg/m^2 pevonedistat (Days 1, 3, and 5 of each 28-day cycle) and azacitidine 75 mg/m^2 (Days 1-5, 8, and 9 of each 28-day cycle). One additional event of Grade 4 increased transaminases was observed in the expansion cohort. This patient was successfully rechallenged at a lower dose of pevonedistat [22].

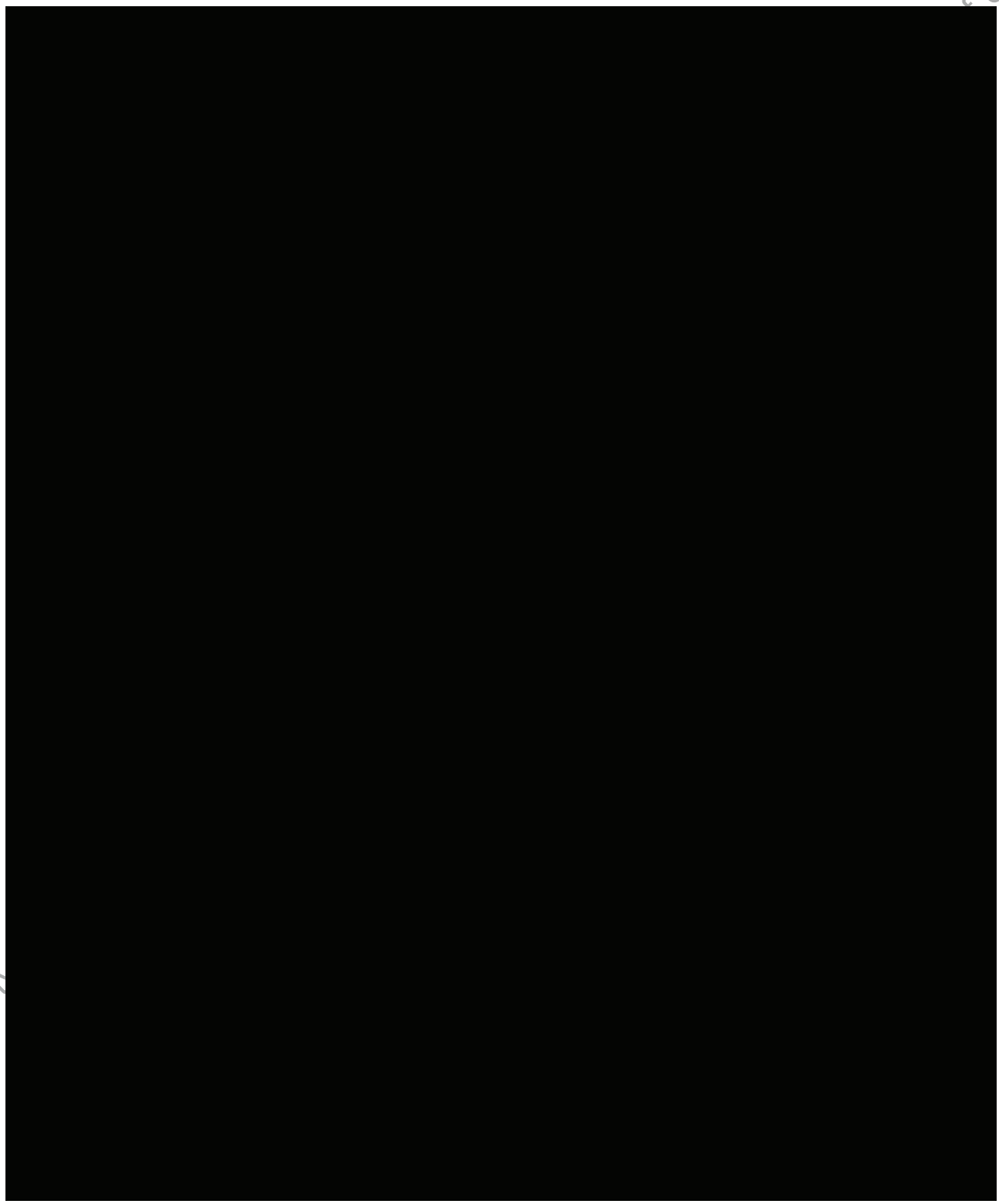
Although the metabolic profiles and disposition pathways of pevonedistat remain to be fully characterized in humans, attributes such as IV administration and body surface area (BSA)-adjusted dosing minimize the likelihood for ethnic-related differences in pevonedistat exposures between populations in Western and Asian countries. [redacted] The starting dose of 25 mg/m^2 pevonedistat (single agent) on Days 1, 3, and 5 is 50% lower than the MTD determined in Western patient populations. The starting dose of 10 mg/m^2 pevonedistat in combination with 75 mg/m^2 azacitidine is 50% lower than the MTD determined in Study C15009. The same azacitidine dose, administration route, and schedule is approved in East Asia (including Japan); based on available PK information, addition of azacitidine did not appear to alter the PK profile of single-agent pevonedistat in the Western patient population. The dose level(s) determined to be safe during the escalation phase of the study will then be expanded to further confirm safety and investigate PK.

1.5.2 Rationale for the Combination of Pevonedistat+Azacitidine

Azacitidine is a chemical analogue of cytidine that is widely used for the treatment of patients with AML. While azacitidine is not approved for AML in the US, it is nonetheless one of the most frequently prescribed agents used to treat elderly, unfit patients with AML. In Japan, azacitidine is used to treat MDS and AML with a low blast percentage (<30%) in the bone marrow. In Taiwan and South Korea, azacitidine is approved for the treatment of high-risk MDS and is used in the treatment of some unfit elderly patients with AML. According to oncologist/hematologist surveys conducted by the sponsor, it is estimated that azacitidine is administered in up to approximately 36% of unfit elderly patients with AML in the US and up to approximately 30% in Europe.

The rationale for combining pevonedistat with azacitidine in patients with AML and MDS is 2-fold: the single-agent activity observed with azacitidine [23] and pevonedistat [24] in

patients with AML or related diseases such as MDS and the preclinical evidence supporting the improved benefit of pevonedistat administered in combination with azacitidine in AML xenograft models; see Section 1.2.2 and the IB for more information. The possible toxicity from each product will be mitigated with multiple risk-mitigation strategies.



1.6 Potential Risks and Benefits

1.6.1 Single-Agent Pevonedistat

Safety information gained from clinical studies of pevonedistat and from toxicology studies in rats and dogs has been used to guide the safety evaluation of pevonedistat. Additional information on risks is provided in the IB.

Based on preliminary findings in single-agent clinical studies and the toxicities noted in the toxicology studies done in rats and dogs, the identified risks of pevonedistat treatment are as follows:

- Increased heart rate.
- Diarrhea.

- Nausea.
- Vomiting.
- Pyrexia.
- Liver function test abnormal.
- Musculoskeletal pain.
- Myalgia.

Please refer to the IB for a discussion of the potential risks associated with pevonedistat.

Hepatotoxicity has been noted following administration of pevonedistat in patients with advanced malignancy, including elevations of liver transaminases, alkaline phosphatase, and bilirubin. Grade 1 through 4 increases in alanine aminotransferase and aspartate aminotransferase have been observed in patients with hematological and solid tumor malignancies receiving pevonedistat as a single agent and in combination with standard-of-care therapies. The patients experiencing these changes in laboratory values have been asymptomatic. 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.

At doses equal to or below 100 mg/m^2 on a Day 1, 3, and 5 or a Day 1, 4, 8, and 11 schedule, there have been reports of changes in serum creatinine from baseline levels of Grade 0 to Grade 1, and from baseline levels of Grade 1 to Grade 2.

Patients must be carefully evaluated at Screening and before each pevonedistat dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Guidance on rehydration is provided in Section 6.8.2.

One patient died of AML complicated by leukostasis within hours after receiving the first dose of pevonedistat (see the IB for additional information). Guidance on management of leukostasis is provided in Section 6.8.1.

A comprehensive review of the clinical trial safety data has shown that toxicity involving multi-organ failure on Cycle 1 Day 1, including SAEs of renal, hepatic, and cardiac failure, some with a fatal outcome, has been observed in pevonedistat studies. Based on the observation that these events are associated with higher pevonedistat doses, the sponsor has determined that newly enrolling patients will receive pevonedistat at doses equal to or below 100 mg/m^2. Our current understanding of the renal toxicity observed with pevonedistat suggests that it is not a primary event but is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response. Patients will be monitored closely for events of multi-organ failure after pevonedistat dosing.

These potential toxicities will be managed by careful, frequent monitoring and intervention, as needed, with supportive care. It is possible that pevonedistat will have toxicities that were not observed in or predicted from the studies completed in rats and dogs, or have not yet been identified in patients.

Patients will be monitored closely for these anticipated and potential toxicities as well as for unanticipated toxicities when they are receiving this agent and for at least 30 days after their last dose. To limit the risks to patients, during dose escalation, a minimum of 3 patients will be enrolled at each new dose level of pevonedistat, as applicable, and observed through the completion of the first cycle before additional patients are treated. In this study, dosing with single-agent pevonedistat is not expected to exceed 44 mg/m^2. Although therapeutic efficacy is a desired outcome of treatment with the study drugs, it is unknown whether patients will benefit from this study. Even if proven efficacious, it is still possible that some patients may receive suboptimal doses of pevonedistat.

See Section 6.8 for information on management of clinical events that may occur with study treatment.

1.6.2 Azacitidine

In worldwide clinical studies, adverse reactions to azacitidine were qualitatively similar between the IV and SC routes of administration [33]. 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 or 2 cycles of SC treatment compared with later cycles 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) [33].

Adverse reactions identified during postmarketing use of azacitidine include interstitial lung disease, tumor lysis syndrome, injection site necrosis, and Sweet syndrome (acute febrile neutrophilic dermatosis) [33].

Refer to the Study Manual for azacitidine prescribing information (PI) or refer to the summary of product characteristics, as applicable, for additional information regarding the anticipated risks and benefits of azacitidine.

1.6.2.1 Anemia, Neutropenia, and Thrombocytopenia

Azacitidine causes anemia, neutropenia, and thrombocytopenia. Complete blood counts should be monitored frequently for response and/or toxicity, at least once prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be adjusted based on nadir counts and hematologic response (see Section 6.4.2.1).

1.6.2.2 Severe Pre-existing Hepatic Impairment

Caution is needed when administering azacitidine in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, with such events occurring most frequently in patients with Baseline albumin levels <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

1.6.2.3 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 chronic myeloid leukemia treated with azacitidine and etoposide.

1.6.3 Pevonedistat+Azacitidine

In the ongoing Study C15009, which administers pevonedistat+azacitidine in patients aged 60 years or older with AML, a total of 13 patients experienced partial remission or better as of 22 January 2015. Five patients had a best response of complete remission, and 8 patients had a best response of partial remission. None of the clinical data observed thus far suggest any lack of efficacy relative to established therapies that would constitute a significant risk to the patient populations in the clinical studies.

As of 22 January 2015, safety data from 42 patients in Study C15009 who received ≥1 dose of pevonedistat+azacitidine indicate that the most common AEs (occurring in ≥25% of patients) include constipation (40%), febrile neutropenia (33%), and anemia, decreased appetite, thrombocytopenia, and fatigue (29% each).

Four patients experienced DLTs (increased LFTs). Because of these events, subsequent patients were dosed at 20 mg/m^2; 2 patients experienced DLTs at this dose.

A total of 27 (64%) patients experienced at least 1 SAE. SAEs that were reported for more than 1 patient were febrile neutropenia (12 patients), pneumonia (4 patients), sepsis (3 patients), and pyrexia and epistaxis (2 patients each).

Eight patients treated with pevonedistat (either 20 mg/m^2 or 30 mg/m^2), discontinued from Study C15009 participation because of a TEAE. Two patients discontinued because of febrile neutropenia; both events were considered related to treatment with pevonedistat. Other events leading to discontinuation that were assessed by study investigators as at least possibly related to study drug treatment were ALT increased, AST increased, blood ALP increased, and multi-organ failure.

Ten on-study deaths (within 30 days of the last dose of study drug) had been reported in Study C15009; none of the deaths was assessed as related to study treatment.

Some of these common events, including myelosuppression with increased susceptibility to infection, bleeding, and anemia, are considered potential risks of pevonedistat because of the occurrence of these events in phase 1 clinical studies in which pevonedistat was administered at high doses. Other common events, such as decreased appetite and febrile neutropenia, are considered potential risks that are confounded by underlying disease or malignancy.

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.

Please 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.

1.6.4 Potential for DDIs

The potential risk of DDIs between pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data (see Section 1.4.1).
Study C15011, a phase 1 DDI study, is currently ongoing and enrolling patients. The study assesses the effect of multiple doses of fluconazole (a moderate CYP3A inhibitor) as well as the effect of multiple doses of itraconazole (a strong CYP3A inhibitor) on the PK, safety, and tolerability of a single dose of IV pevonedistat. As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored because 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.

No formal clinical assessments of DDIs between azacitidine and other agents have been conducted. Please consult the azacitidine PI in the Study Manual for additional information.

See Section 6.5 for information on concomitant medications that are prohibited during this study.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are as follows:

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

2.2 Secondary Objective

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

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints are as follows:

- Safety parameters: AEs, SAEs, DLTs during Cycle 1 (dose-escalation phase only), and abnormal laboratory values reported.
- Summary statistics of PK parameters of pevonedistat, including single-dose maximum (peak) concentration (C_{max}), area under the plasma concentration- time curve during a dosing interval (AUC_{τ}), and CL, when administered alone and during concomitant administration of azacitidine during Cycle 1 (dose escalation and expansion phases).

3.2 Secondary Endpoints

The secondary endpoints are as follows:

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

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This is a multicenter, open-label, phase 1/1b dose escalation and expansion study of pevonedistat administered IV as a single agent and in combination with azacitidine in adult East Asian patients with World Health Organization (WHO)-defined AML or HR MDS (Revised International Prognostic Scoring System [IPSS-R] very high/high/intermediate) (see Section 15.1).

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

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

In parallel with the opening of enrollment for the second dose level in the Single-Agent Arm, enrollment will begin for the first dose level of the Combination Arm. The Combination Arm will include East Asian patients with R/R AML or R/R HR MDS (including R/R nonproliferative CMML) as well as previously untreated AML or HR MDS (including nonproliferative CMML). In the pevonedistat+azacitidine Combination Arm, each 28-day treatment cycle includes the following: treatment with pevonedistat (starting dose of 10 mg/m^2) on Days 1, 3, and 5; treatment with azacitidine (75 mg/m^2) on Days 1 through 5, and 8 through 9; and a rest period of 19 days. Samples for PK will be collected during Cycle 1. Enrollment in the Combination Arm will not begin until 3 patients have successfully completed Cycle 1 of the 25 mg/m^2 Single-Agent Arm.

Patients, including those who achieve a CR, may receive pevonedistat and/or azacitidine until they experience disease progression or symptomatic deterioration. Study drug may be discontinued if a patient experiences study drug-related toxicities or if, in the opinion of the investigator or sponsor, continuation on study may jeopardize the safety of the patient.

Patients may discontinue therapy at any time for any reason. Patients will attend the End of Study (EOS) visit for safety 30 days after receiving their last dose of study drug.

The 3+3 approach will be used during the dose-escalation phase, as detailed in Section 6.3. The dose level(s) determined to be safe during the dose-escalation phase of the study may then be expanded to as many as 12 patients in total to further confirm safety and investigate PK. Based on the geographic distribution of patients in the dose escalation/expansion phases (Single-agent and/or Combination Arms) and emerging PK and safety data, additional patients may be added in the expansion phase, as needed, to further characterize the PK, safety, and tolerability in a particular East Asian geographic region.

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

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

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [34]. DLTs are defined in Section 6.2.

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

Serial blood samples for determination of the plasma concentration of pevonedistat will be obtained during Cycle 1 at prespecified time points as described in the Schedules of Events and in Section 7.4.17. [redacted] Treatment-emergent resistance will also be monitored. [redacted]

[redacted]

Disease response assessments will be conducted using International Working Group (IWG) criteria [35] for AML and modified IWG criteria [36] for MDS (including CMML).

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

4.2 Number of Patients

Approximately 37 patients will be enrolled in this study from 6 to 9 study centers in East Asian countries including but not limited to Japan, Taiwan, and South Korea. Enrollment is achieved when the first dose of any study drug has been administered.

4.3 Duration of Study

Patients, including those who achieve a clinical response, may receive study treatment until they experience disease progression, until their treatment is discontinued for any other reason outlined in Section 7.7, or until the study is stopped. Patients will be considered to have completed the study if they have completed study treatment and performed the EOS visit or until the sponsor terminates the study.

Patients will be followed for 30 days (+10 days) after the last dose of study drug to permit further detection of any treatment-related AEs. Analyses for the clinical study report will be conducted after the study is complete.

It is anticipated that enrollment into this study will last for approximately 24 months. The estimated total study duration includes 24 months of accrual plus the additional follow-up of 10 months after the last patient is enrolled.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. East Asian patients aged 18 years or older (if local regulation requires a minimum age for informed consent of more than 18 years, then patients must be the minimum age or older per the local regulation) when written study informed consent is obtained must meet 1 of the following diagnosis criteria for either the Single-Agent Arm or the Combination Arm:

    - Single-Agent Arm:

        - Male and female patients with WHO-defined AML [1], 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 (R/R) and are not candidates for potentially curative treatment, or

        - Male and female patients with WHO-defined MDS [2] that meets the International Prognostic Scoring System [IPSS-R] criteria for the very high, high, or intermediate risk group (Section 15.1) [3], for whom standard curative, life-prolonging treatment does not exist or is no longer effective (R/R), or

        - Male and female patients with WHO-defined CMML-2 or CMML-1 that meets the IPSS-R criteria for the very high, high, or intermediate risk group (Section 15.1), [3] for whom standard curative, life-prolonging treatment does not exist or is no longer effective (R/R); CMML-1 patients must have bone marrow blasts ≥5% [2].

    - Combination Arm:

        - Male and female patients with WHO-defined AML [1], 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 (R/R) and are not candidates for potentially curative treatment, or

        - Male and female patients aged 60 years or older with previously untreated AML who have bone marrow blasts <30% and who are not candidates for standard induction chemotherapy, or

- Male and female patients with WHO-defined MDS [2] that meets the IPSS-R criteria for the very high, high, or intermediate risk group (Section 15.1) [3], for whom standard curative, life-prolonging treatment does not exist or is no longer effective (R/R), or

- Male and female patients with previously untreated MDS [2] that meets the IPSS-R criteria for the very high, high, or intermediate risk group (Section 15.1) [3].

- Male and female patients with WHO-defined CMML-2 or CMML-1 that meets the IPSS-R criteria for the very high, high, or intermediate risk group (Section 15.1) [3]; CMML-1 patients must have bone marrow blasts ≥5% [2].

2. *For all AML patients:* white blood cell (WBC) count <50,000/µL before administration of the first dose of pevonedistat on Cycle 1 Day 1. Note: hydroxyurea may be used to control the level of WBC counts to no lower than 10,000/µL during the study.

3. *For the CMML patients:* morphologically confirmed nonproliferative CMML, ie, WBC <20,000/µL before administration of the first dose of pevonedistat on Cycle 1 Day 1.

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (see Section 15.2).

5. Clinical laboratory values within the following parameters within 3 days before the first dose of study drug:

   - Albumin ≥2.7 g/dL.
   - Total bilirubin ≤upper limit of normal (ULN).
   - Alanine aminotransferase and AST ≤2.5×ULN.
   - Calculated creatinine clearance ≥50 mL/min (see Section 15.3).
   - Hemoglobin >8 g/dL. Patients may be transfused to achieve this value. Elevated indirect bilirubin due to post-transfusion hemolysis is not exclusionary.

6. Able to undergo bone marrow aspiration and biopsy at Screening.

7. Suitable venous access for the study-required blood sampling (ie, including PK and pharmacodynamic sampling).

8. Female patients who:

   - Are postmenopausal (not due to other medical reasons; see Section 15.9) for at least 1 year before the Screening visit, or
   - Are surgically sterile, or
   - If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (See Section 15.10), at the same time, from the time of signing the informed consent through 4 months after the last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm), 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, and 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, 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 pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm), 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 for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

5.2 Exclusion Criteria

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

1. Acute promyelocytic leukemia (as diagnosed by morphologic examination of bone marrow, by fluorescent in situ hybridization or cytogenetics [t(15:17)] of peripheral blood or bone marrow, or by other accepted analysis) or AML associated with t(9;22) karyotypes or molecular evidence of such translocations.
2. *(Combination Arm only)* More than 3 prior lines of therapy.
3. *(Combination Arm only)* Prior therapy with hypomethylating agents (eg, azacitidine, decitabine).
4. Eligibility for a hematopoietic stem cell transplant.
5. Female patients who are in the lactation period, even if they discontinue breastfeeding, or who have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.
6. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures.
7. Treatment with any investigational products within 14 days before the first dose of any study drug.
8. *(Combination Arm only)* Known hypersensitivity to azacitidine or mannitol.
9. Active, uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, septicemia, or methicillin-resistant *Staphylococcus aureus* infection.
10. Major surgery within 14 days before first dose or a scheduled surgery during the study period.
11. Life-threatening illness unrelated to cancer.
12. Known central nervous system involvement.
13. Prothrombin time (PT) or activated partial thromboplastin time (aPTT) >1.5×ULN or active uncontrolled coagulopathy or bleeding disorder.

14. Known human immunodeficiency virus (HIV) seropositive.

15. Known hepatitis B surface antigen (HBsAg) seropositive or known or suspected active hepatitis C infection. Note: patients who have isolated positive hepatitis B core antibody (HBcAb) and/or positive hepatitis B surface antibody (HBsAb) (ie, in the setting of negative HBsAg) may be included if they have an undetectable hepatitis B viral load. Patients who have positive hepatitis C antibody may be included if they have an undetectable hepatitis C viral load.

16. Known hepatic cirrhosis or severe pre-existing hepatic impairment.

17. Known cardiopulmonary disease, defined as unstable angina, clinically significant arrhythmia, or congestive heart failure (New York Heart Association Class III or IV; see Section 15.4), myocardial infarction within 6 months of first dose of study drug, or severe pulmonary arterial hypertension.

18. Left ventricular ejection fraction (LVEF) <50% as assessed by echocardiogram or multiple-gated acquisition scan.

19. Treatment with moderate or strong CYP3A inhibitors or inducers within 7 days before the first dose of pevonedistat as described in Section 15.5. Patients must have no history of amiodarone use in the 6 months before the first dose of pevonedistat.

20. Systemic antineoplastic therapy or radiotherapy within 14 days before the first dose of any study drug, except for hydroxyurea.

21. Female patients who intend to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm).

22. Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm).

6. STUDY DRUG

6.1 Study Drug Administration

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

If required by local regulations or local clinical guidelines or preferred by the investigator, study drugs and protocol assessments may be administered in an in-patient setting during Cycle 1.

The amount of study drug to be administered will be based on BSA. BSA will be calculated using a standard formula (see example in Section 15.6) 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.

Patients will receive pevonedistat diluted with 5% dextrose 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 entire content of the pevonedistat IV bag will be infused at a constant rate over 60 minutes, although the infusion may be slowed or stopped and restarted for any associated infusion-related reactions. To ensure that all the pevonedistat is administered, the infusion line will be flushed with saline 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. The total time from drug reconstitution to the end of infusion must not exceed 6 hours.

All doses must be taken as outlined in the Schedules of Events. For Cycle 1, every effort should be made to administer study drug(s) around the same time of the day. No doses should be missed or delayed during Cycle 1 due to patient scheduling. Dosing of pevonedistat should always be performed on schedule. However, occasional changes in azacitidine dosing are allowable after the first cycle: 1) a single dose can be administered within a window of ±2 clinic days of specified study day for holidays and other administrative reasons, and 2) a single dose can be missed for patient vacations. If extenuating circumstances prevent a patient from getting azacitidine treatment within this time, the patient may continue the study only with the written permission of the sponsor.

Planned doses and dosing schedules will be as shown in Table 6.a; additional information is provided in Section 6.4. However, the date of Day 1 dosing may be modified by up to 2 days (for Cycle 2 and beyond) to accommodate inclement weather, holidays, vacations, or other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment within this time, the patient may continue the study only with the written permission of the sponsor.

The start and end time of IV infusion should be recorded accurately, particularly when PK assessments are also performed.

6.1.1 Single-agent Pevonedistat Arm

Patients in the Single-Agent Arm will receive pevonedistat administered via 60-minute IV infusion on Days 1, 3, and 5 of each 21-day cycle; planned dose levels are described in Table 6.a. All doses must be taken as outlined in the Schedules of Events.

6.1.2 Pevonedistat+Azacitidine Combination Arm – Azacitidine Dosing

Patients in the Combination Arm will receive pevonedistat in combination with azacitidine, as outlined in the Schedules of Events. Planned dose levels are provided in Table 6.a.

Patients in the Combination Arm will receive azacitidine (75 mg/m^2 [IV during Cycle 1; IV or SC in Cycles 2 and beyond, per the investigator's choice]) on Days 1 through 5 and Days 8 through 9 of each 28-day treatment cycle (regardless of whether the patient is hospitalized during treatment). Please see the Vidaza (azacitidine) PI in the Study Manual for details on azacitidine administration.

In addition, patients will receive pevonedistat administered via 60-minute IV infusion on Days 1, 3, and 5 of each 28-day cycle. 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 SC azacitidine or between 30 and 60 minutes after completion of administration of IV azacitidine. After Cycle 1, the investigator, without approval of the sponsor or designee, may choose to switch the route of azacitidine administration based on standard of care, clinical preference, or convenience.

6.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [34]. These criteria are provided in the Study Manual. DLTs will be defined as

any of the following events that are considered by the investigator to be at least possibly related to therapy with the study drug(s):

- Grade 3 or greater nausea and/or emesis despite the use of optimal antiemetic prophylaxis. Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-hydroxytryptamine 3 serotonin receptor antagonist and a corticosteroid given in standard doses and according to standard schedules.
- Grade 3 or greater diarrhea that occurs despite maximal supportive therapy.
- Grade 3 or greater arthralgia/myalgia despite the use of optimal analgesia.
- Any other Grade 3 or greater nonhematologic toxicity with the following exceptions:
    - Brief (<1 week) fatigue.
    - Hypophosphatemia.
- Persistent elevations of transaminases and bilirubin above Grade 2 beyond 2 days between doses will be considered dose limiting.
- Other study drug-related nonhematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require a dose reduction or discontinuation of therapy with pevonedistat.

Note that Grade 3 or greater hematologic toxicities, including Grade 3 or 4 febrile neutropenia, are not considered to be DLTs unless they meet the following criteria:

- A delay in the initiation of Cycle 2 due to a lack of adequate recovery from treatment-related toxicity (recovery to ≤Grade 1 or to patient's Baseline values):
    - Of more than 4 weeks due to hematologic toxicity believed not related to leukemic infiltration. Bone marrow evaluation may be required.
    - Of more than 2 weeks due to nonhematologic toxicities.

Although AEs meeting the protocol-specified definition of DLTs may occur at any point during treatment, only those AEs meeting the DLT definition occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose

level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

6.3 Dose Escalation Rules

This study will use a 3+3 design in the dose escalation phase for the pevonedistat Single-Agent Arm and pevonedistat+azacitidine Combination Arm. The escalation starts with single-agent pevonedistat (group of 3 patients) at 25 mg/m^2 (Table 6.a). If this dose is safe and tolerable, the dose escalation will then be split into 2 independent arms: 1 for single-agent pevonedistat (1 additional planned dose level: 44 mg/m^2) and the other for the pevonedistat+azacitidine combination (2 planned dose levels: 10 and 20 mg/m^2), which will lead to confirmation of safety of single-agent pevonedistat and the RP2/3D for pevonedistat given in combination. Note that no intra-patient dose escalation is permitted. Specific rules for the 3+3 algorithm are as follows:

1. If 0 of 3 patients experiences DLT, dose escalation will proceed to the next higher dose level, at which 3 patients will be enrolled.

2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level. Escalation will continue if 1 of 6 patients experiences DLT.

3. If 2 or more patients at any dose level experience DLT, dosing will stop, and 1 of the following options will be chosen by the sponsor:

    - Three additional patients will be added to the previous dose level, or declare the lower dose level as tolerable dose if 6 patients have already been dosed.

    - An intermediate dose between 25 and 44 mg/m^2 may be tested for single-agent pevonedistat escalation; for the pevonedistat+azacitidine combination, an intermediate dose of 15 mg/m^2 may be considered.

4. If 0 of 3 patients experiences DLT at the highest dose level, 3 additional patients will be enrolled at the same dose level (for a total of 6 patients in the dose-escalation phase at the highest dose level).

Escalation beyond 44 mg/m^2 when given as single agent or 20 mg/m^2 when combined with azacitidine is not expected to be necessary in this study. However, if pevonedistat exposures are unexpectedly lower than anticipated in the East Asian populations, and no DLTs have

occurred in the dose-escalation groups, the pevonedistat dose may be escalated further after discussion between the investigator and the sponsor based on available PK and safety data.

Table 6.a Planned Dose Levels

Single-Agent Arm Dose Level	Dose (unit)	Dose-Escalation Phase (# of patients)	Expansion Phase
1	25 mg/m^2	3~6	The highest tolerated dose level may be expanded up to 12 patients in total.
2	44 mg/m^2	0~6	
Combination Arm Dose Level	**Dose (unit)**	**Dose-Escalation Phase (# of patients)**	**Expansion Phase**
1	10 mg/m^2 (in combination with azacitidine 75 mg/m^2)	0~6	The highest tolerated dose level may be expanded up to 12 patients in total.
2	20 mg/m^2 (in combination with azacitidine 75 mg/m^2)	0~6	

Evaluation of intermediate doses and/or expansion of any dose level studied during dose escalation are permissible, based on emerging data and following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, PK, or pharmacodynamics of pevonedistat.

The dose escalation decision and expansion flowchart is provided in Section 15.7.

Patients not receiving all doses of pevonedistat or azacitidine in Cycle 1 for reasons other than DLTs will be replaced within the dose group.

6.4 Dose Modification Guidelines

6.4.1 Criteria for Retreatment and Dose Delays

Retreatment Within a Cycle

If dosing of either drug is delayed for safety reasons, retreatment may be resumed upon resolution of the safety condition. For pevonedistat, a minimum of 1 full calendar day between any 2 doses should be maintained (eg, Day 1 [Monday] and Day 3 [Wednesday]). In each cycle, a maximum of 3 doses of pevonedistat and 7 doses azacitidine (as applicable) should not be exceeded.

If dosing is interrupted within a cycle because of toxicity, and if, in the opinion of the investigator and the sponsor or designee, it is in the patient's interest to continue therapy

with the study drug(s), then after recovery of the toxicity or toxicities in question to ≤Grade 1 or to the patient's Baseline values, the dose of study drug may be reduced. For specific guidelines on azacitidine and pevonedistat dose reductions, see Sections 6.4.2 and 6.4.3).

Initiation of a New Cycle

Treatment with study drugs will be repeated every 21 days (Single-Agent Arm) or 28 days (Combination Arm). For therapy to resume, toxicity considered related to treatment with study drugs must have resolved to ≤Grade 1, to the patient's Baseline values, or to a level considered acceptable by the investigator after discussion with the sponsor or designee.

If a patient fails to meet the criteria for retreatment, 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 reevaluated to determine whether the criteria for retreatment have been met. For a delay of >2 weeks, a discussion with the sponsor is required to determine whether the patient may continue treatment. A dose reduction (as detailed in Sections 6.4.2 and 6.4.3) would be triggered should treatment be delayed for >2 weeks because of incomplete recovery from treatment-related nonhematologic toxicity or >4 weeks because of incomplete recovery from treatment-related hematologic toxicity that is not related to leukemic infiltration.

6.4.2 Dose Modification for Hematologic Toxicities

A delay in the initiation of a cycle by >4 weeks because of lack of recovery from treatment-related hematologic toxicity that is not related to leukemic infiltration will trigger a dose reduction, if treatment resumes. Recovery is defined as resolved to ≤Grade 1, to the patient's Baseline values, or to a level considered acceptable by the investigator after discussion with the medical monitor. If indicated, bone marrow evaluation will be performed to establish whether continued myelosuppression is related to persistent or progressing leukemic infiltration.

6.4.2.1 Azacitidine

For hematologic toxicities >Grade 1, azacitidine should be reduced in accordance with Table 6.b or Table 6.c and/or institutional guidelines, with prior agreement by the sponsor or designee.

For patients with WBC count ≥3.0×10^9/L, absolute neutrophil count (ANC) ≥1.5×10^9/L, and platelets ≥75.0×10^9/L, the azacitidine dose should be adjusted based on nadir counts for any given cycle as detailed in Table 6.b.

Table 6.b Azacitidine Dose Adjustment Based on Hematology Laboratory Value Nadir Counts

Nadir Counts		
Absolute Neutrophil Count (×10^9/L)	**Platelets (×10^9/L)**	**% Dose in the Next Course**
<0.5	<25.0	50%
0.5-1.5	25.0-50.0	67%
>1.5	>50.0	100%

Source: Vidaza PI [33].
Abbreviations: ANC=absolute neutrophil count, PI=prescribing information, WBC=white blood cell.
This table applies to patients with the following Baseline counts: WBC count ≥3.0×10^9/L, ANC ≥1.5×10^9/L, and platelets ≥75.0×10^9/L.

For patients with Baseline counts of WBC <3.0×10^9/L and/or ANC <1.5×10^9/L and/or platelets <75.0×10^9/L, dose adjustments should be based on nadir counts and bone marrow aspirate cellularity at the time of the nadir, as noted in Table 6.c, unless there is clear improvement in differentiation at the time of the next cycle (eg, the percentage of mature granulocytes is higher and ANC is higher than at the onset of that course); in this case, the dose of the current treatment should be continued.

Table 6.c Azacitidine Dose Adjustment Based on Bone Marrow Aspirate Cellularity

	Bone Marrow Aspirate Cellularity at the Time of Nadir (%)		
Nadir Decrease in WBC or Platelet Counts from Baseline (%)	**30-60**	**15-30**	**<15**
	% Dose in the Next Course		
50-75	100	50	33
>75	75	50	33

Source: Vidaza PI [33].
Abbreviations: ANC=absolute neutrophil count, PI=Prescribing Information, WBC=white blood cell.
This table applies to patients with Baseline counts of WBC <3.0×10^9/L and/or ANC <1.5×10^9/L and/or platelets <75.0×10^9/L.

If a nadir as defined in Table 6.c has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are >25% above the nadir and rising. If a >25% increase above the nadir is not seen

by Day 28, counts should be reassessed every 7 days. If a 25% increase is not seen by Day 42, the patient should be treated with 50% of the scheduled azacitidine dose.

6.4.2.2 Pevonedistat

For patients who develop symptoms of leukostasis, pevonedistat should be held until leukostasis is treated. Treatment may include leukapheresis and hydroxyurea according to institutional guidelines. As soon as WBC count is <50,000/μL, pevonedistat may be restarted, following agreement with sponsor.

For patients whose Baseline counts are WBC $<3.0\times10^9$/L, ANC $<1.5\times10^9$/L, or platelets $<75.0\times10^9$/L, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir (if available), unless there is clear improvement in differentiation (percentage of mature granulocytes and ANC are higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

6.4.3 Dose Modification for Nonhematologic Toxicities

6.4.3.1 Azacitidine

Azacitidine Dose Adjustment Based on Renal Function and Serum Electrolytes

For renal toxicities, specifically elevated creatinine >Grade 1, azacitidine should be reduced in accordance with the PI [33] and/or institutional guidelines. Similarly, if unexplained elevations in serum creatinine (to >1.5× the ULN) or blood urea nitrogen (BUN) occur, the next cycle should be delayed until values return to normal or baseline, and the dose should be reduced by 50% on the next treatment course. See the Vidaza PI in the Study Manual for more details.

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 value.

6.4.3.2 Pevonedistat

Pevonedistat Dose Adjustment Based on Serum Transaminases and Total Bilirubin

Based on current data from Studies C15003 and C15009, it is anticipated that in some patients liver function tests ([LFTs] AST, ALT, and occasionally bilirubin) may be elevated for approximately 48 hours following the end of pevonedistat infusion on Cycle 1 Day 1.

Dosing will continue only if there is no evidence of DLT before each dose, only if any elevations in the serum transaminases are Grade 1 or less, and only if any elevations in bilirubin are ≤1.5×ULN. Dosing may be delayed for 1 additional day, without reduction in dose, for resolution of effects on serum transaminases to Grade 1 and bilirubin to ≤1.5×ULN. Persistent elevations of transaminases and bilirubin above Grade 2 beyond 2 days between doses will be considered dose limiting.

For therapy to resume, toxicity considered related to treatment with the study drugs must have resolved to ≤Grade 1 or to the patient's Baseline values. If dosing is interrupted within a cycle because of toxicity, and if, in the opinion of the investigator and the sponsor, it is in the patient's interest to continue therapy with the study drugs, then after recovery of the toxicity or toxicities in question to ≤Grade 1 or to the patient's Baseline values, the dose of pevonedistat may be reduced.

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, monitored, and treated according to institutional guidelines.

Pevonedistat Dose Adjustment for Other Toxicities

For treatment-related nonhematologic toxicities >Grade 1, the dose of pevonedistat should be reduced by 1 dose level (if applicable) after discussion with sponsor.

6.5 Excluded Concomitant Medications and Procedures

Medications that are generally excluded but are allowed with certain exceptions listed in Table 6.d.

The use of moderate and strong CYP3A inhibitors is prohibited for 7 days prior to the first dose of study drug(s) only during treatment Cycle 1 for both study arms. In treatment

Cycle 2 and beyond, the use of moderate and strong CYP3A inhibitors is permitted. See Section 15.5 for additional details of specific CYP3A inhibitors.

Table 6.d Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	May be used judiciously but should not exceed a dose of 2 g in 24 hours.
Systemic antineoplastic therapy, except for hydroxyurea	Hydroxyurea dosing may be adjusted to control the level of WBC counts to no lower than 10,000 while on study treatment. The dosing of hydroxyurea and changes to dosing of hydroxyurea must be recorded.
Moderate and strong CYP3A inhibitors (see Section 15.5)	Excluded for 7 days prior to first dose of study drug(s) and during treatment Cycle 1 only for both the Single-Agent Arm and the Combination Arm. **Limited use of the azole antifungal agents voriconazole and fluconazole, and ciprofloxacin during Cycle 1 is permitted only if clinically necessary and no suitable alternative exists.** The patient may receive the azole antifungal or ciprofloxacin from 24 hours after the last pevonedistat dose until 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), and Friday (Day 5) schedule, then the azole antifungal or ciprofloxacin may be administered from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle. For treatment Cycle 2 and beyond, the use of moderate and strong CYP3A inhibitors is permitted for both the Single-Agent Arm and the Combination Arm. See Section 15.5.
Moderate and strong CYP3A inducers [including St. John's wort (Hypericum perforatum)] (see Section 15.5)	Excluded from the study.
Known BCRP inhibitors (ie, cyclosporine and eltrombopag [Promacta])	Generally excluded **but limited use is permitted only if clinically necessary and no suitable alternative exists.** The patient may receive the BCRP inhibitor from 24 hours after the last pevonedistat dose until 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), and Friday (Day 5) schedule, then the BCRP inhibitor may be administered from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle.
Known P-gp inhibitors (ie, **azithromycin [Zithromax],** captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor)	Generally excluded during the study **but limited use is permitted only if clinically necessary and no suitable alternative exists.** The patient may receive the P-gp inhibitor from 24 hours after the last pevonedistat dose until 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), and Friday (Day 5) schedule, then the P-gp inhibitor may be administered from the Saturday after

Table 6.d Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
	the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle.
Myeloid growth factors (eg, G-CSF, GM-CSF)	Generally excluded but allowed if deemed medically necessary, after discussion with sponsor.
Erythropoietin	Generally excluded but allowed if approved locally and deemed medically necessary, after discussion with sponsor.
Any investigational agent other than pevonedistat, including agents commercially available for indications other than AML or MDS (eg, eltrombopag, romiplostim)	Excluded during the study.

Abbreviations: AML=acute myeloid leukemia, BCRP=breast cancer-resistance protein, CYP=cytochrome P450, G-CSF=granulocyte colony stimulating factor, GM-CSF=granulocyte macrophage colony-stimulating factor, P-gp=P-glycoprotein; WBC=white blood cell.

6.6 Permitted Concomitant Medications and Procedures

Medications and procedures that are specifically permitted during the study are listed in Table 6.e.

Table 6.e Permitted Concomitant Medications and Procedures

Therapy	Comment
Antiemetics for azacitidine	May be administered according to institutional guidelines.
Hydroxyurea	Dosing of hydroxyurea may be adjusted to control the level of WBC counts to no lower than 10,000 while on treatment with study drugs. The dosing of hydroxyurea and changes to dosing of hydroxyurea should be recorded. Patients may start or restart treatment with hydroxyurea during the study.
Moderate and strong CYP3A inhibitors	For treatment Cycle 2 and beyond, the use of moderate and strong CYP3A inhibitors is permitted for both the Single-Agent Arm and the Combination Arm. See Section 15.5. Use of moderate and strong CYP3A inhibitors are excluded for 7 days prior to first dose of study drug(s) and during treatment Cycle 1 only for both the Single-Agent Arm and the Combination Arm.
RBC transfusion	To be considered for all patients with anemia, especially those with hemoglobin values <8 g/dL. RBC transfusion should occur at least 1 day prior to investigational product administration.

Abbreviations: CYP=cytochrome P450; RBC=red blood cell; WBC=white blood cell.

6.7 Precautions and Restrictions

Concomitant medications and procedures that are excluded or must be used with caution are described in Sections 6.5 and 6.6, respectively.

Certain situations may warrant further caution, such as modifying the dose of study drug(s). Dose modification guidelines are provided in Section 6.4.

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 Section 15.10) through defined periods during and after study treatment as specified below.

1) Use only contraceptive methods that are locally approved in each country

2) Female patients must meet 1 of the following:

- Postmenopausal (not due to other medical reasons; see Section 15.10) for at least 1 year before the Screening visit, or
- Surgically sterile, or
- If they are of childbearing potential (as defined in Section 7.4.13), agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm), 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.)
- Female patients must agree not to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of pevonedistat (for patients in the

Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm).

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug (if barrier methods are not locally approved to be used by males, then their female partners should use effective contraceptive methods as described in the above), 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 for the female partner], 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 not to donate sperm during the course of this study or 4 months after receiving their last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm).

6.8 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.

The most common adverse drug reactions for azacitidine are described in the Vidaza PI [33]. Please see the Vidaza PI in the Study Manual as applicable for details regarding the management of clinical events attributed to azacitidine.

Common AEs reported for patients receiving pevonedistat are listed in Section 1.6.1. Also refer to the most recent IB.

6.8.1 Leukostasis in Patients Receiving Pevonedistat

Pevonedistat treatment should be withheld for patients who develop symptoms of leukostasis (see Section 6.4.2.2). Treatment may include leukapheresis and hydroxyurea administration, per institutional guidelines. When the WBC of the patient is <50,000/μL and

symptoms are improved, pevonedistat treatment may be restarted after consulting with the sponsor or designee.

6.8.2 Hemodynamic Compromise in Patients Receiving Pevonedistat

It is essential that the patients receiving pevonedistat are carefully evaluated at Screening and before each pevonedistat dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Patients who experience an untoward reaction with pevonedistat 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/hour 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; each RBC transfusion should 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.

Patients who experience an untoward reaction with pevonedistat should be followed closely on subsequent dosing.

6.8.3 Hepatotoxicity in Patients Receiving Pevonedistat

Please refer to Section 6.4.3.2 for dose modifications or delay for LFT elevations in patients receiving pevonedistat. Frequent follow up of liver enzymes, bilirubin, and coagulation profile (INR) as well as supportive care are recommended according to institutional practice. Concomitant medications that may contribute to liver toxicity should be held if possible.

6.8.4 Hematologic Toxicity in Patients Receiving Pevonedistat

Please refer to Section 6.4.2.2 for dose adjustments for hematologic toxicity in patients receiving pevonedistat. Supportive care and transfusion should be considered according to institutional practice at the medical discretion of the investigator.

6.8.5 Extravasation

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.

6.9 Blinding and Unblinding

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

6.10 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.

6.10.1 Pevonedistat

The drug product is labeled pevonedistat (MLN4924 Injection).

[redacted]

Details are available in the IB.

6.10.2 Azacitidine

Commercially available azacitidine is supplied as lyophilized powder in 100-mg, single-use vials. Refer to the Vidaza PI in the Study Manual for additional information regarding azacitidine [33].

6.11 Preparation, Reconstitution, and Dispensation

Pevonedistat and azacitidine are anticancer drugs; as with other potentially toxic compounds, caution should be exercised when handling pevonedistat and azacitidine.

Pevonedistat solution for injection vials should be removed and allowed to equilibrate to room temperature before dilution. Using aseptic technique, the specified amount of drug product solution should be removed and administered per the information provided in the Pharmacy Manual. For a detailed preparation of the infusion, refer to the Directions for Investigational Drug Use document located in the Pharmacy Manual. The pevonedistat prepared IV bag must be used within 6 hours. The vial must not be shaken at any time during dose preparation. The bag, needle, and syringe must be disposed of in a proper biohazard container.

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

Instructions for the preparation, reconstitution, and dispensation of azacitidine are provided in the Vidaza PI in the Study Manual.

6.12 Packaging and Labeling

Pevonedistat will be provided in 10-mL USP Type I glass vials. Each USP Type I glass vial nominally contains 5 mL of compounded sterile solution, sealed with a Teflon coated 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.

6.13 Storage, Handling, and Accountability

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

Vials of pevonedistat solution for injection are to be stored at 2°C to 8°C.

Details of the storage and handling of azacitidine are provided in the Vidaza PI (available in the Study Manual).

A drug dispensing log, including records of drug received from the sponsor and drug administered to the patients, will be provided and kept at the study site. Disposal instructions are provided in the Pharmacy Manual.

7. 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.

If required by local regulations or local clinical guidelines or preferred by the investigator, study drugs and protocol assessments may be administered in an in-patient setting during Cycle 1.

7.1 Study Personnel and Organizations

The contact information for the medical monitor for this study, the central laboratories and any additional clinical laboratories, the contract research organization team, and the interactive voice/web response system may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 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.

7.3 Treatment Arm Assignments

No randomization or stratification will be performed in this study. This study incorporates dose escalation and expansion phases of pevonedistat as single agent or combined with azacitidine. After the first single-agent dose level is deemed to be safe, single agent and combination dose escalation will be performed independently and simultaneously.

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

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

7.4 Study Procedures

Refer to the Schedules of Events for timing of assessments. Separate subschedules for Cycle 1 and for Cycle 2 and beyond are provided for each treatment arm. Additional details are provided as necessary in the sections that follow and in the Study and Laboratory Manuals. When applicable, specific visit windows for assessments are provided in the footnotes to the study schedules. Day 1 of Cycle 2 and beyond may be modified by up to 2 days to accommodate inclement weather, holidays, vacations, or other administrative reasons.

7.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

As allowed by regulations, the date of birth, race, ethnicity, and sex of the patient will be recorded during Screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 7.4.10.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at Screening. A symptom-directed physical exam will be completed per standard of care at the times specified in the Schedules of Events and as clinically indicated.

7.4.5 Patient Height

Height will be measured only during Screening.

7.4.6 Patient Weight

Weight will be measured at the time points listed in the Schedules of Events.

7.4.7 ECOG Performance Status

ECOG performance status (Section 15.2) will be assessed at the times specified in the Schedules of Events.

7.4.8 Vital Signs

Vital sign measurements, including diastolic and systolic blood pressure, heart rate, and body temperature, will be taken according to the Schedules of Events and as clinically indicated. At the predose and 1 hour postdose time points on Cycle 1 Day 1, orthostatic blood pressure and heart rate measurements will be taken with the patient in a supine position and then standing, after waiting 3 to 4 minutes. At all other time points, a sitting position is preferred for the collection of vital signs. If a supine position is used, it should be used consistently for the same patient throughout the study.

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.

7.4.9 Electrocardiogram

A 12-lead ECG will be administered at the time points specified in the Schedules of Events.

7.4.10 Concomitant Medications and Procedures

Concomitant medications and procedures (including 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 study drug(s). See Section 6.5 and Section 6.6 for details regarding excluded and permitted

concomitant medications and procedures, respectively, including recording requirements for hydroxyurea and transfusions.

7.4.11 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally.

Hematology

Blood samples for analysis of the following hematologic parameters will be obtained as specified in the Schedules of Events and more frequently if clinically indicated.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential, including circulating blast count
- Lymphoblasts
- Myelocytes
- Neutrophils (ANC)
  Note: ANC may be calculated from the leukocyte count with differential count; see Section 15.8.

Coagulation

Blood samples for a coagulation panel will be obtained as specified in the Schedules of Events. The coagulation panel will include prothrombin time (international normalized ratio) and activated partial thromboplastin time.

Clinical Chemistry

Blood samples for analysis of the following serum chemistry parameters will be obtained as specified in the Schedules of Events and more frequently if clinically indicated.

Complete Serum Chemistry Panel

- BUN
- Creatinine
- Bilirubin (direct)
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2 if available as part of chemistry panel from venous blood draw)
- Magnesium

Select Serum Chemistry Panel

- BUN
- Creatinine
- Bilirubin (total)
- ALP
- AST
- ALT
- LDH

Urinalysis

Urine samples for urinalysis will be obtained as specified in the Schedules of Events and more frequently if clinically indicated.

Urinalysis With Microscopic Analysis

- Turbidity and color
- pH
- Specific gravity
- Protein
- Ketones
- Occult blood
- Nitrite
- Phosphate
- Leukocyte esterase
- Microscopic assessment of leukocytes, erythrocytes, bacteria, casts, and crystals

7.4.12 Echocardiogram

LVEF should be assessed by echocardiography or multiple-gated acquisition scan at Screening.

7.4.13 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening and within 3 days prior to the first dose of study drug. The results from these tests must be available and negative before the first dose of study drug is administered. If the Cycle 1 Day 1 serum pregnancy results are not available before dosing, a urine pregnancy test may be performed.

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

1. Those who have not undergone hysterectomy or bilateral oophorectomy, and

2. Those who have not had natural menopause for 12 consecutive months or longer (eg, 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).

7.4.14 Hepatitis Testing

Hepatitis testing will be performed at Screening. As appropriate, and according to local guidelines for the management of hepatitis B virus infection, hepatitis B virus (HBV) screening may include the following: HBsAg, HBsAb, HBcAb, and HBV viral load. Hepatitis C virus (HCV) screening is to include the anti-HCV antibody (HCVAb); if positive, this test should be followed by a reactive viral load test. Patients, who are HBsAg negative, and HBsAb and/or HBcAb positive, and/or HCVAb positive with negative viral load at screening, enrolled in this study will be monitored by assessment of viral load (HBV-DNA; HCV-RNA) as needed and based on local institutional guidelines. If a patient's viral load becomes positive for HBV and/or HCV at any time during the study, and infection is confirmed, the patient will be withdrawn from the study and treated per local institutional guidelines.

7.4.15 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedules of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.16 Enrollment

A patient is considered to be enrolled in the study when the first dose of any study drug has been administered.

Procedures for the completion of the enrollment information are described in the Pharmacy and Study Manual.

7.4.17 Pharmacokinetic Measurements

Blood samples (approximately 3 mL) for the determination of plasma concentrations of pevonedistat will be collected from all patients during Cycle 1 of the study. 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.

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 that occur close to the infusion.

To ensure that the measurements are representative of plasma exposure, 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.

7.4.17.1 Single-Agent Arm

In all patients in the Single-Agent Arm, blood samples for PK analysis will be collected during Cycle 1 at the times specified in the Serial Pharmacokinetic Sample Breakdown - Single-Agent Pevonedistat Arm.

7.4.17.2 Combination Arm

In all patients in the Combination Arm, blood samples for PK analysis will be collected during Cycle 1 at the times specified in the Serial Pharmacokinetic Sample Breakdown - Pevonedistat+Azacitidine Combination Arm.

[redacted]

[redacted]

[redacted]

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

7.4.19 Disease Assessment

Disease assessments will be performed in conjunction with bone marrow assessments (see the Schedules of Events).

7.4.19.1 Revised Recommendations of the IWG Response Criteria for AML

In patients with AML, assessment of disease response will follow the criteria outlined in the Revised Recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [35]. When possible, the same qualified physician will interpret results to reduce variability.

Investigators are encouraged to consult the reference for a more detailed explanation of the response criteria.

CR, CR with incomplete blood count recovery (CRi), and PR are defined using the following criteria:

> **Morphologic CR**: A CR designation requires that the patient achieve the morphologic leukemia-free state and have an ANC of more than 1,000/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 CRi**: After chemotherapy, some patients fulfill all of the criteria for CR except for residual neutropenia (<1,000/µL) or thrombocytopenia (<100,000/µL).
>
> **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 between 5% and 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%, then it 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.

Definition of Progressive Disease

Because the IWG criteria for AML do not provide a standardized definition for progressive disease (PD) [35], in this protocol, PD is defined as 1 of the following:

- >50% increase in bone marrow blasts from Baseline value (to a maximum of 100% blasts).
- >50% increase in circulating blasts from Baseline value (to a maximum of 100% 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.

Note: When deciding PD for patients with high blasts at Baseline (eg, >70% blasts), investigators are encouraged to use best medical judgement based on the patient's overall clinical profile and in consideration of local institutional guidelines.

Definition of 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.

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 6 responders in the single-agent pevonedistat study in R/R AML 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 decreased. 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.

Therefore, it might be in the best interest of the patient to continue study treatment in spite of transient elevation on bone marrow blast counts that could potentially qualify as PD. In those cases, a discussion between the investigator and the sponsor is required before the patient can continue study treatment.

7.4.19.2 IWG Response Criteria for MDS

The revised recommendations of the IWG for response criteria in myelodysplasia will be used for assessment of disease response in patients with MDS, including CMML [36]. Investigators are encouraged to consult the reference for a more detailed explanation of the response criteria.

Table 7.a Modified IWG Response Criteria for Altering Natural History of MDS

Category	Response Criteria (responses must last at least 4 weeks)
Complete remission	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%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥50% from pretreatment but still >5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤5% myeloblasts and decrease by ≥50% from pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in the percentage of bone marrow blasts, or progression to a more advanced MDS or CMML FAB/WHO subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence

Table 7.a Modified IWG Response Criteria for Altering Natural History of MDS

Category	Response Criteria (responses must last at least 4 weeks)
Cytogenic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥50% increase in blasts to >5% blasts 5% to 10% blasts: ≥50% increase to >10% blasts 10% to 20% blasts: ≥50% increase to >20% blasts 20% to 30% blasts: ≥50% increase to >30% blasts Any of the following: At least a 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥2 g/dL Transfusion dependence

Source: Cheson et al 2006 [36].

Abbreviations: CMML=chronic myelomonocytic leukemia, CR=complete remission, FAB=French-American-British, Hgb=hemoglobin, HI=hematologic improvement, IWG=International Working Group, MDS=myelodysplastic syndromes, PR=partial remission, WHO=World Health Organization.

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

b In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. 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.

Table 7.b Response Criteria for Hematologic Improvement

Hematologic Improvement[a]	Response criteria (responses must be at least 8 weeks)
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 per 8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for an Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment, $<100\times10^9$/L)	Absolute increase of $\geq30\times10^9$/L for patients starting with $>20\times10^9$/L platelets Increase from $<20\times10^9$/L to $>20\times10^9$/L and by at least 100%
Neutrophil response (pretreatment, $<1.0\times10^9$/L)	At least 100% increase and an absolute increase $>0.5\times10^9$/L
Progression or relapse after HI[b]	At least 1 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

Abbreviations: Hgb=hemoglobin, HI=hematologic improvement, 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, repeated courses of chemotherapy, gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

If a patient has an increase of >50% marrow blasts but, in the opinion of the investigator is deriving clinical benefit, the patient may continue with treatment after discussion with the sponsor.

7.4.20 Bone Marrow Aspirate and Biopsy Collection for Disease Assessment and Molecular Analyses

A bone marrow biopsy (in addition to bone marrow aspirate) is required only at Screening to confirm diagnosis; for all other time points, only bone marrow aspirate will be collected unless major changes in the patient's underlying hematological disease are suspected. 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. Historical results from up to 2 months prior to enrollment are acceptable for disease classification, but not disease status. If historical results do not show either t(15;17) or t(9;22), then these results can be used to ensure eligibility, provided a formal confirmatory report is sent as soon as it becomes available.

Bone marrow aspirate collection at Screening is required for study entry to assess disease burden, cytogenetics, and karyotype. Bone marrow aspirates will also be collected at the end of Cycle 2 and Cycle 4 (Day 21 [-6 days] for the Single-Agent Arm and any time between Days 20 and 28 for the Combination Arm, provided that the disease assessment is available before Day 1 of the following cycle) to assess disease response. After Cycle 4, bone marrow aspirates will be performed after completion of every third cycle (eg, Cycle 7, Cycle 10, etc.), and at the EOS visit for patients who withdraw for reasons other than disease progression. [redacted].

[redacted]

7.5 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.

7.6 Completion of Treatment

Patients will be considered to have completed treatment if they discontinue treatment for any of the reasons outlined in Section 7.7.

There are no subsequent protocol-specified assessments after the completion of study treatment.

The EOS visit is to be completed 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy (other than hydroxyurea), if that occurs sooner. See the Schedules of Events for appropriate assessments during the EOS visit.

7.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Patients will receive treatment until PD or discontinuation for any other reason, including those outlined below. **Patients may be allowed to remain on study, after discussion between the investigator and the medical monitor, even if they meet the criteria for PD based only on bone marrow blast counts.**

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

- AE.
- Protocol violation.
- Progressive disease.
- Symptomatic deterioration.
- Initiation of hematopoietic stem cell transplant.
- Study terminated by sponsor.
- Withdrawal by subject.
- 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 Schedules of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

7.7.1 Patient Replacement:

Patients in the escalation phase who are withdrawn from the treatment or experience dosing delay or dosing reduction in either pevonedistat or azacitidine during Cycle 1 for reasons other than DLT will be replaced.

7.8 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 subject.
- Death.
- Progressive disease.

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.

7.9 Completion of Study

Patients 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.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

Analyses will be primarily descriptive in nature. No formal statistical hypothesis testing will be performed. A formal statistical analysis plan will be developed and finalized before database lock.

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 non-missing values) per category for categorical data, unless specified otherwise.

8.1.1 Determination of Sample Size

This study will use a 3+3 design in the dose escalation phase for single-agent pevonedistat and the pevonedistat+azacitidine combination. The escalation starts with single-agent pevonedistat (group of 3 patients) at 25 mg/m^2. If this dose is safe and tolerable, the escalation will then be split into 2 independent arms: 1 for single-agent pevonedistat and the other for the pevonedistat+azacitidine combination. At the highest tolerated dose level, an additional 3 patients will be added during the dose escalation phase to confirm safety and tolerability. Assuming this study schema and also assuming an additional 6 patients in the dose expansion phase, the estimated number of patients for the study via simulation is 30 to

33. To further allow for other considerations, such as the number of PK-evaluable patients and number of patients required per country or East Asian race group at the highest dose level, the estimated number of patients to be enrolled in this study is approximately 37.

8.1.2 Randomization and Stratification

No randomization or stratification will be performed in this study.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- **Safety population:** patients who receive at least 1 dose of study drug will be used for all safety analyses and efficacy analyses.
- **PK population:** patients who have sufficient dosing in Cycle 1 and pevonedistat concentration-time data to reliably estimate PK parameters by noncompartmental analysis methods and who have not received any excluded concomitant medications per the protocol.
- **Response-Evaluable population:** patients who receive at least 1 dose of study drug, have a Baseline disease assessment, and have at least 1 post-Baseline disease assessment will be used for analyses of response.
- **DLT-Evaluable population:** patients who either experience DLT during Cycle 1 or receive all scheduled doses of study drug in Cycle 1 without DLT.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed unless specified otherwise. The relevance of missing sample data will be assessed.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and Baseline characteristics, including gender, age, race, weight, height, Baseline disease characteristics, and other parameters as appropriate, will be summarized in a descriptive fashion.

8.1.6 Efficacy Analysis

Efficacy measures will include disease response and duration of disease response. Analysis of all efficacy measures will be descriptive. Disease response in patients with AML will be based on the ORR (CR+PR [for AML] and CR+PR+HI [for MDS]) and CR as determined by the investigator using the Revised Recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (Section 7.4.19.1).

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

Disease response in patients with MDS will be based on the best overall response as determined by the investigator using the revised IWG response criteria for MDS (Section 7.4.19.2) [36]. The duration of response will be defined in patients with disease response (CR or PR) as the time between the first documentation of response and disease progression. Responders without disease progression will be censored at the last clinical assessment of response.

8.1.7 Pharmacokinetics [redacted]

PK Analysis

Individual values and descriptive statistics of pevonedistat plasma concentration-time data and PK parameters will be listed and tabulated by treatment arm, dose level, and study day (Single-agent and Combination Arms). PK parameters of pevonedistat alone or combined with azacitidine in individual patients will be estimated using noncompartmental methods. PK parameters include, but are not limited to, C_{max}, T_{max}, the area under the plasma concentration-time curve from 0 to the last measurable concentration (AUC_{last}), AUC_{τ}, CL, volume of distribution at steady-state (Vss), $t_{1/2}$, area under the plasma concentration-time curve from 0 to infinity (AUC_{∞}), and accumulation ratio, as data permit.

For each of the treatment arms, individual and mean pevonedistat plasma concentration-time data will be listed by patient identification number and plotted over time (including nominal and actual times) by dose level and study day using linear and logarithmic scales. The relationships between dose and C_{max} or AUC will also be explored graphically for dose proportionality, as deemed appropriate.

[redacted]

8.1.8 Safety Analysis

The incidence of DLT will be tabulated for each dose group and treatment (single agent or combination). In addition, to assess the relationship between toxicities and pevonedistat dose, the preferred term of individual toxicities will be summarized by their frequency and intensity for each dose group and treatment. The DLT-Evaluable population will be used for the analysis of DLTs.

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

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days (+10 days) after the last dose of study drug will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Treatment-emergent Grade 3, Grade 4, and Grade 5 AEs (presented by grade and overall).
- Drug-related treatment-emergent Grade 3, Grade 4, and Grade 5 AEs (presented by grade and overall).

- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients).

- SAEs.

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or 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.

Descriptive statistics for the actual values (and/or the changes from Baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE version 4.03 grade from Baseline to the worst post-Baseline value. Graphical displays of key safety parameters, such as scatter plots of Baseline versus worst post-Baseline values, may be used to understand the pevonedistat safety profile.

All concomitant medications collected from Screening through the study period will be classified to preferred terms according to the WHO drug dictionary.

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

8.1.9 Interim Analysis

As this is a phase 1/1b study, no formal interim analysis is planned. Safety and PK data will be reviewed on an ongoing basis during the dose escalation and expansion phases of the study.

8.2 Pharmacokinetic Modeling

Individual pevonedistat plasma concentration-time data may be combined with other study data (including dosing information and patient-specific covariates) from previous and future pevonedistat clinical trials to create an analysis dataset for population PK analysis. Details of the modeling approach will be provided in a separate analysis plan, and the results of these analyses will be reported separately.

9. STUDY COMMITTEES

9.1 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) has been formed to periodically monitor the overall conduct of studies within the pevonedistat program, including to review accumulating clinical study data and safety data (both clinical and nonclinical) and to make recommendations to Millennium to safeguard the interests of study participants. Additionally, the IDMC may make recommendations relating to the selection, recruitment, and retention of study participants, patient management, improving adherence to protocol-specified regimens, and procedures for data management and quality control.

Further details regarding the IDMC will be provided in the IDMC charter.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event 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 Adverse Event 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 Serious Adverse Event 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 which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below 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 1 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 4.03, effective date 14 June 2010 [34]. 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 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 Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/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 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

BI Medical, Inc
Korea: 00798-8171773
Taiwan: 00801-814742
Japan: 0120-490-849

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and ethics committees as applicable, in accordance with national regulations in the countries where the study is conducted. Specifically in the EU, the sponsor will ensure that all relevant information from SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the regulatory authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than 7 days after knowledge by the sponsor of such a case, and relevant follow-up information is subsequently communicated within an

additional 8 days. All other SUSARs shall be reported to the regulatory authorities concerned and to the Ethics Committee concerned as soon as possible within a maximum of 15 days of first knowledge by the sponsor. The sponsor will also inform all the investigators in the clinical trial.

Once a year throughout the conduct of the clinical trial, the sponsor will provide the regulatory authorities in whose territory the clinical trial is being conducted and the Ethics Committees with a listing of all SUSARs that have occurred over the past year and a report of the subjects' safety.

Planned hospital admissions or surgical procedures for an illness or disease that existed 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 intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [34]. The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of Adverse Events and Period of Observation

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

- AEs will be reported from administration of the first dose of study drug through 30 days (+10 days) after administration of the last dose of study drug and recorded in the eCRFs.

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug 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 Millennium Department of Pharmacovigilance or designee. SAEs 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).

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 faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). 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 faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure 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.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium,

or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints

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 contact the Medical Information Call Center/Dohmen Life Science Services and report the complaint. The contact information is as follows:

Medical Information Call Center:	Dohmen Life Science Services
Phone:	1-866-835-2233
Fax:	1-800-881-6092
E-mail:	GlobalOncologyMedinfo@takeda.com
Hours:	Mon-Fri, 9 AM–7 PM, ET

Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to BI Medical, Inc. (refer to Section 10.2).

11.12 Closure of the Study

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enroll patients at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Insufficient, incomplete, and/or unevaluable data.
- Determination of efficacy based on interim analysis.
- Plans to modify, suspend, or discontinue the development of the study drug.

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

11.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study

records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

12. USE OF INFORMATION

All information regarding study drug supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of study drug and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

13. INVESTIGATOR AGREEMENT

I have read Protocol Pevonedistat-1012 Amendment 03: A Phase 1/1b, Open-label Study of Pevonedistat (MLN4924, TAK-924) as Single Agent and in Combination with Azacitidine in Adult East Asian Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS).

I agree to conduct the study as detailed herein and in compliance with International Council for Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

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15. APPENDICES

15.1 Revised International Prognostic Scoring System for MDS

Tables are adapted from mds-foundation.org/ipss-r-calculator/, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes Risk Assessment Calculator, Accessed 05 January 2015, based on Greenberg et al. [3].

Table 15.a IPSS-R Prognostic Score Values

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	≤2		>2 to <5		5 to 10%	>10%	
Hemoglobin	≥10		8 to <10	<8			
Platelets	≥100	50 to <100	<50				
ANC	≥0.8	<0.8					

Source: Greenberg et al, Blood 120: 2454, 2012 [3].

Abbreviations: ANC=absolute neutrophil count, BM=bone marrow, IPSS-R=Revised International Prognostic Scoring System.

[redacted]

Table 15.c IPSS-R Prognostic Risk Categories/Scores

Risk Category	Risk Score
Very low	≤1.5
Low	>1.5 to 3
Intermediate	>3 to 4.5
High	>4.5 to 6
Very high	>6

Source: Greenberg et al, Blood 120: 2454, 2012 [3].
Abbreviation: IPSS-R=Revised International Prognostic Scoring System.

15.2 Eastern Cooperative Oncology Group 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 MM, et al. 1982 [38].

15.3 Cockcroft-Gault Equation

For male subjects:

$$\text{Creatinine clearance} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For female subjects:

$$\text{Creatinine clearance} = \frac{0.85(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

15.4 New York Heart Association Classification of Cardiac Disease

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.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9 ed. Boston, MA: Little, Brown & Co; 1994 [39].

15.5 Excluded CYP3A Inhibitors and Inducers

Note that HIV medications that are strong or moderate CYP3A inhibitors or inducers are not included in this list because HIV-positive patients are excluded from study participation.

15.5.1 Classification of CYP3A Inhibitors

Use of moderate and strong CYP3A inhibitors listed in Table 15.d should be avoided for 7 days prior to initiation of pevonedistat therapy and for the duration of Cycle 1 only. The use of moderate and strong CYP3A inhibitors is permitted in treatment Cycle 2 and beyond. The moderate CYP3A inhibitor amiodarone has a long half-life (mean of 58 days). Consequently, amiodarone must be discontinued 6 months before the first dose of pevonedistat.

Table 15.d In Vivo Inhibitors of CYP3A

Strong Inhibitors 5-fold increase in AUC	Moderate Inhibitors 2-fold, but <5-fold increase in AUC
Clarithromycin	Amiodarone
Itraconazole	Aprepitant
Ketoconazole	Diltiazem
Nefazodone	Erythromycin
Voriconazole[a]	Ciprofloxacin[a]
Posaconazole	Cimetidine
Telithromycin	Fluconazole[a]
Conivaptan	Verapamil
	Tofisopam
	Dronedarone

Abbreviations: AUC=area under the plasma concentration-time curve, CYP=cytochrome P450.

This is not an exhaustive list; please refer to the following sources:
medicine.iupui.edu/flockhart/table.htm and
fda.gov/CDER/drug/drugInteractions/tableSubstrates.htm for additional information.

a Permitted only if the patient's clinical condition requires the use of the azole antifungal agents, voriconazole and fluconazole, or ciprofloxacin. The patient may receive the azole antifungal or ciprofloxacin from 24 hours after the last pevonedistat dose to 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), and Friday (Day 5) schedule, then the azole antifungal or ciprofloxacin may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle.

15.5.2 Classification of CYP3A Inducers

Use of the moderate and strong CYP3A inducers listed in Table 15.e should be avoided during pevonedistat therapy.

Table 15.e In Vivo Inducers of CYP3A

Strong Inducers ≥80% decrease in AUC	**Moderate Inducers 50% to 80% decrease in AUC**
Carbamazepine	Bosentan
Phenytoin	Modafinil
Phenobarbital	Nafcillin
Primidone	
Rifabutin	
Rifampin	
Rifapentine	
St. John's wort	

Abbreviations: AUC=area under the plasma concentration versus time curve, CYP=cytochrome P450.
This is not an exhaustive list; please refer to the following sources:
medicine.iupui.edu/flockhart/table htm and
fda.gov/CDER/drug/drugInteractions/tableSubstrates.htm for additional information.

15.6 Body Surface Area Calculation

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

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

OR

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

15.7 3+3 Dose Escalation and Expansion Flowchart

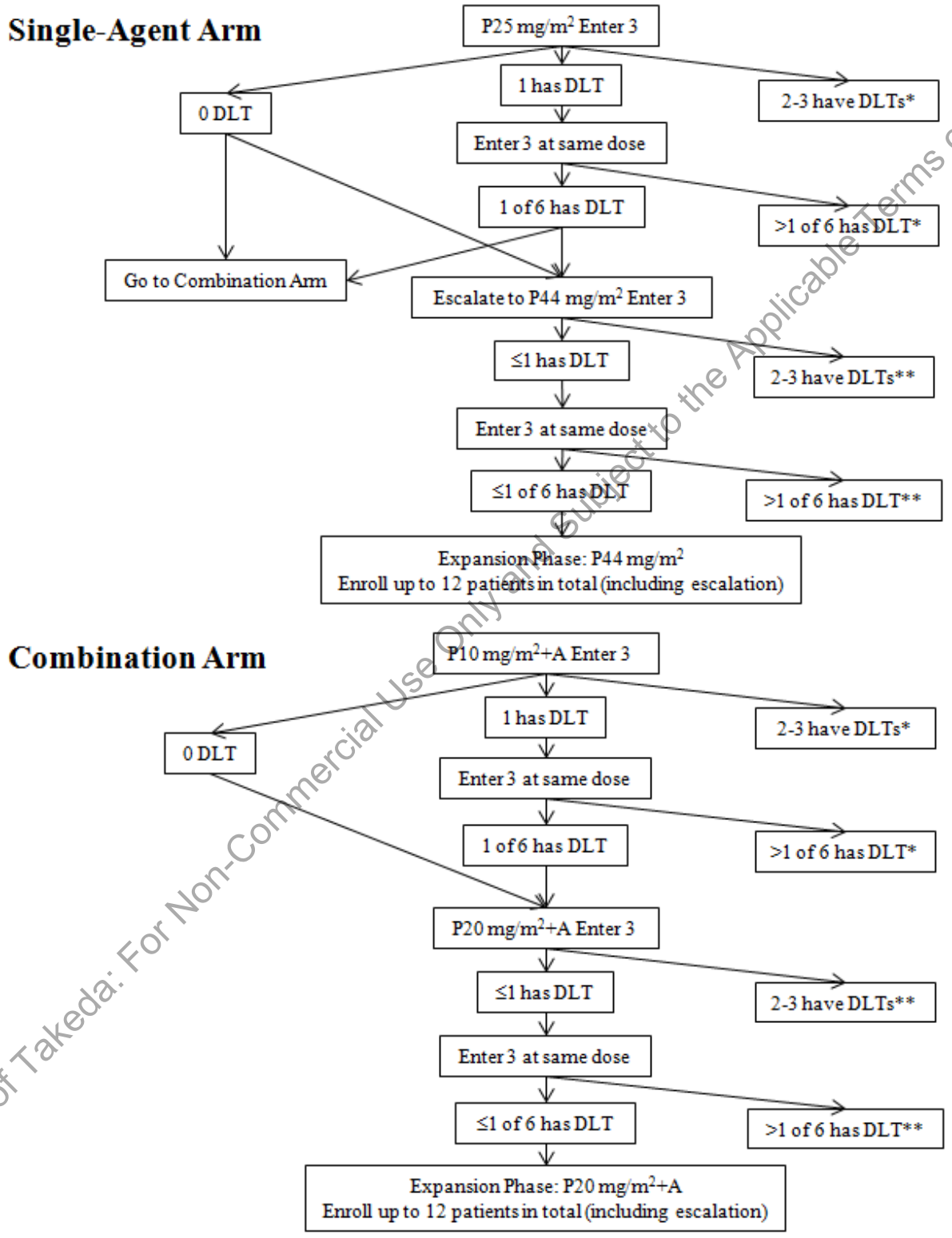

Figure footnotes appear on next page.

Section 15.7 Figure Footnotes

Abbreviations: A=azacitidine 75 mg/m^2, DLT=dose-limiting toxicity, P10=pevonedistat 10 mg/m^2, P20=pevonedistat 20 mg/m^2, P25=pevonedistat 25 mg/m^2, P44=pevonedistat 44 mg/m^2.

* dosing stop.

** dosing stop, 1 of the following options will be chosen by the sponsor:

- Three additional patients will be added to the previous dose level, or declare the lower dose level as tolerable dose if 6 patients have already been dosed.
- An intermediate dose between 25 and 44 mg/m^2 may be tested for single-agent arm; for the combination arm, an intermediate dose of 15 mg/m^2 may be considered.

15.8 Absolute Neutrophil Count Calculation

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

Example:

If total leukocyte count=4.3; segmented neutrophils=48%; band neutrophils=2%,

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

15.9 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 (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_ CTFG_Contraception.pdf

15.10 Methods of Contraception Considered to be Effective

Acceptable Contraception Methods 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]
- Vasectomised partner.[b,c]
- Sexual abstinence.[d]

Contraception 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]

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

[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] Vasectomised 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 vasectomised 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 trial 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) are also considered acceptable, but not highly effective birth control methods.

15.11 Amendment 01 Rationale and Purposes

Rationale for Amendment 01

The original protocol was approved by the signatories on 24 February 2015. Modifications and revisions to the text were required to clarify information. The study has not enrolled any patients.

The rationale for instituting the 4-month requirement for female contraception after the last dose of study drug in women of childbearing potential is primarily because some may experience longer than the average 28-day menstrual cycle, and the extension to 4 months would adequately and safely cover these patients. In addition, pevonedistat is a first-in-class molecule warranting a more cautious approach, and the 4-month requirement for women matches the contraception recommendation for men.

[redacted]

The rationale for revising the definition of progressive disease is based on requests from the Study C15009 investigators to clarify disease response in the rare event that a bone marrow sample is not available.

Purposes for Amendment 01

The purposes of this amendment are to:

- Update the product research name.
- Update the protocol approval signatories.
- Change the site-generated mutation data collected at Screening to a site-generated mutation report.
- Change the site-generated cytogenetics data collected at Screening to a site-generated cytogenetics report.
- Add full chemistry, hematology, and coagulation laboratory evaluations for patients in Japan who receive study drugs and protocol assessments in an in-patient setting during Cycle 1.
- Clarify that WBC count must be <50,000/µL before administration of pevonedistat.
- Clarify that the Day 15 chemistry and hematology sample collection window is ±1 day.
- Add blood phosphate tests to Week 1 Day 5 of each cycle from Cycle 2 and beyond.
- Clarify that urine samples for safety assessments will be analyzed at the local laboratory.
- Change the time for electrocardiogram evaluation immediately after the infusion of pevonedistat.
- Update the section on clinical data from the ongoing study with pevonedistat plus azacitidine.

- Specify that a phase 1 drug-drug interactions (DDI) study is ongoing in the pharmacokinetics of pevonedistat/DDI risk assessment section.
- Update the section on the rationale for the combination of pevonedistat and azacitidine.
- Change the observed increases in alanine aminotransferase and aspartate aminotransferase to Grade 1 through 4.
- Update the risk language regarding increases in serum creatinine.
- Clarify that pevonedistat escalation beyond 44 mg/m^2 when given as single agent may be allowed.
- Update the section on the risks and benefits from the ongoing study with pevonedistat plus azacitidine.
- Clarify that the study population will include East Asian patients only.
- Clarify that the primary endpoints will include summary statistics of PK parameters.
- Specify that the Combination Arm will include East Asian patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) or R/R higher-risk (HR) myelodysplastic syndromes (MDS) (including R/R chronic myelomonocytic leukemia [CMML]) and previously untreated AML or HR MDS (including CMML).
- Clarify that for inclusion into the study, patients must be aged 18 years or older and meet diagnostic criteria when written study informed consent is obtained.
- Specify that hydroxyurea may be used to control WBC counts no lower than 10,000/μL rather than circulating leukemic blast cell counts.
- Revise the inclusion criteria to include the diagnosis of nonproliferative CMML.
- Update exclusion criteria to exclude patients with prothrombin time or activated partial thromboplastin time >1.5 times the upper limit of the normal range.
- Add persistent elevations of transaminases and bilirubin above Grade 2 beyond 2 days between doses as a dose-limiting toxicity.
- Specify in the text that the delay period for initiation of a cycle will be >4 weeks.
- Clarify the limited use of known P-glycoprotein inhibitors during the study.
- Specify that the use of investigational agents for the treatment of MDS will be excluded during the study.
- Modify the period of contraception use after the last dose of study drug for women of childbearing potential to 4 months.
- Correct the description of the investigational product formulation.
- Correct the drug product labeling.
- Delete coordinating investigators from study personnel.
- Remove gamma glutamyl transferase from the complete serum chemistry panel.
- Remove urobilinogen from the urinalysis with microscopic analysis.
- Add urine safety assessments to the Clinical Laboratory Evaluations section.
- Change the sample collected at Screening for genotyping variations in genes encoding drug-metabolizing enzymes from peripheral blood samples to buccal swabs.

- [redacted]
- [redacted].
- Revise the definition of progressive disease.
- Clarify the definition of the Response-Evaluable population.
- Add the suspected unexpected serious adverse reactions reporting section to expand the sponsor's responsibilities for reporting expected and unexpected adverse events.
- Update contact information for product complaints.
- Correct typographical errors, punctuation, grammar, and formatting.

15.12 Amendment 02 Rationale and Purposes

Rationale for Amendment 02

This protocol was revised to comply with requests received from the Japan Pharmaceuticals and Medical Devices Agency.

Purposes for Amendment 02

The purposes of this amendment are to:

- Clarify the minimum age for eligibility to comply with local regulations.
- Clarify definition of postmenopausal for eligibility.
- Specify that patients who are lactating and interrupt breastfeeding will not be eligible to participate in the study.
- Clarify that patients with isolated positive hepatitis B core antibody (HBcAb) and/or positive hepatitis B surface antibody (HBsAb) may be included if they have an undetectable hepatitis B viral load.
- Clarify that patients who have positive hepatitis C antibody (HCVAb) may be included if they have an undetectable hepatitis C viral load.
- Specify that patients who are hepatitis B surface antigen negative, and HBsAb and/or HBcAb positive, and/or HCVAb positive with negative viral load at screening will be monitored by assessment of viral load (HBV-DNA; HCV-RNA) as needed and based on local institutional guidelines.
- Specify that patients whose viral load becomes positive for HBV and/or HCV at any time during the study will be withdrawn from the study.
- Clarify the number of patients to be included at each dose level.
- Clarify that intake of St John's wort is to be excluded during the study.
- Specify that intake of Erythropoietin may be allowed if approved locally and deemed medically necessary.
- Provide the definition of women of childbearing potential.
- [redacted]
- [redacted]
- Provide examples of effective female birth control methods.
- Clarify that if barrier methods are not locally approved for male patients, then their female partners should use effective contraceptive methods.
- Correct typographical errors, punctuation, grammar, and formatting.

15.13 Amendment 03 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Amendment 03 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Adjust contraception requirements to be consistent with CTFG recommendations.

The primary change occurs in Section 6.7 Precautions and Restrictions:

Initial wording:

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 effective methods of contraception through defined periods during and after study treatment as specified below.

1) Some examples of effective contraceptive methods include intrauterine devices (IUD), hormonal contraceptives, condom and others
2) Use only contraceptive methods that are locally approved in each country
3) Female patients must meet 1 of the following:
   - Postmenopausal (not due to other medical reasons) for at least 1 year before the Screening visit, or
   - Surgically sterile, or
   - If they are of childbearing potential (as defined in Section 7.4.13), agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm), 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] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug (if barrier methods are not locally approved to be

	used by males, then their female partners should use effective contraceptive methods as described in the above), 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 for the female partner] and withdrawal are not acceptable methods of contraception.)
Amended or new wording:	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 Section 15.10)** through defined periods during and after study treatment as specified below. ~~1) Some examples of effective contraceptive methods include intrauterine devices (IUD), hormonal contraceptives, condom and others~~ 2) Use only contraceptive methods that are locally approved in each country 3) Female patients must meet 1 of the following: • Postmenopausal (not due to other medical reasons**; see Section 15.10)** for at least 1 year before the Screening visit, or • Surgically sterile, or • If they are of childbearing potential (as defined in Section 7.4.13), agree to practice ~~2~~**1 highly** effective method~~s~~ **and 1 additional effective (barrier) method** of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm), 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~~] and~~**],** withdrawal**, spermicides only, and lactational amenorrhea** are not acceptable methods of contraception**. Female and male condoms should not be used together**.) • **Female patients must agree not to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for**

patients in the Combination Arm).

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug (if barrier methods are not locally approved to be used by males, then their female partners should use effective contraceptive methods as described in the above), 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 for the female partner~~] and~~**],** 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 not to donate sperm during the course of this study or 4 months after receiving their last dose of pevonedistat (for patients in the Single-Agent Arm), or through 4 months after the last dose of azacitidine (for patients in the Combination Arm).**

Rationale for Change:

The update in contraception requirements was included for consistency with program-wide updates.

The following sections also contain this change:

- Section 5.1 Inclusion Criteria.
- Section 5.2 Exclusion Criteria.
- Section 15.10 Methods of Contraception Considered to be Effective.

Change 2: Clarify that when additional electrocardiograms will be performed immediately following pevonedistat administration, there is up to a 10-minute window for measurement.

The primary change occurs in the Schedules of Events for the Single-Agent Arm, Cycle 1, footnote f:

Initial wording:	f	A 12-lead ECG will be performed during Screening; predose on Cycle 1 Day 1; and on Cycle 1 Days 1, 3, and 5, 6 hours (± 1 hour) after the completion of the pevonedistat infusion. An additional ECG will also be performed on Cycle 1 Day 1 immediately following pevonedistat administration (within 5-10 minutes after the completion of pevonedistat infusion).

Amended or new wording:	f A 12-lead ECG will be performed during Screening; predose on Cycle 1 Day 1; and on Cycle 1 Days 1, 3, and 5, 6 hours (± 1 hour) after the completion of the pevonedistat infusion. An additional ECG will also be performed on Cycle 1 Day 1 immediately following pevonedistat administration (~~within 5~~ **up to** 10 minutes after the completion of pevonedistat infusion).

Rationale for Change:

Text describing the window of measurement was revised for clarity.

The Schedules of Events for the Combination Arm, Cycle 1, footnote h, also contains this change.

Change 3: Clarify that vital signs assessment includes a ±10-minute window.

The primary change occurs in the Schedules of Events for the Single-Agent Arm, Cycle 1, footnote e:

Initial wording:	e Vital sign measurements, including body temperature, diastolic and systolic blood pressure, and heart rate, will be obtained during Screening; on all dosing days (predose [20 minutes before pevonedistat infusion ±10 minutes] and 1 hour [±10 minutes] after the completion of pevonedistat infusion); on Day 2, Day 8, and Day 15; at EOS; and as clinically indicated. The Day 1 vital sign measurements will be taken pre-infusion and 30 minutes, 1 hour, 4 hours, and 6 hours after the completion of pevonedistat infusion.
Amended or new wording:	e Vital sign measurements, including body temperature, diastolic and systolic blood pressure, and heart rate, will be obtained during Screening; on all dosing days (predose [~~20 minutes~~ before pevonedistat infusion ~~±10 minutes~~] and 1 hour [±10 minutes] after the completion of pevonedistat infusion); on Days 2, 8, and 15; at EOS; and as clinically indicated. The Day 1 vital sign measurements will be taken pre-infusion and 30 minutes **(±10 minutes)**, 1 hour **(±10 minutes)**, 4 hours **(±10 minutes)**, and 6 hours **(±10 minutes)** after the completion of pevonedistat infusion.

Rationale for Change:

The addition of the ±10-minute window was made to allow flexibility in vital sign measurement.

The following sections also contain this change:

- The Schedules of Events for the Single-Agent Arm, Cycle 2 and Beyond, footnote d.
- The Schedules of Events for the Combination Arm, Cycle 1, footnote g.
- The Schedules of Events for the Combination Arm, Cycle 2 and Beyond, footnote g.

Change 4: Allow multiple-gated acquisition scans to also be used to assess left ventricular ejection fraction.

The primary change occurs in Section 7.4.12 Echocardiogram:

Added text: **Echocardiogram**

LVEF should be assessed by echocardiography **or multiple-gated acquisition scan** at Screening.

Rationale for Change:

Multiple-gated acquisition scans were included to allow flexibility in the assessment of left ventricular ejection fraction.

The following sections also contain this change:

- The Schedules of Events for the Single-Agent Arm, Cycle 1, footnote m.
- The Schedules of Events for the Combination Arm, Cycle 1, footnote n.
- Section 5.2 Exclusion Criteria.

Change 5: Clarify that the period of observation and collection for serious adverse events (SAEs) includes a +10-day window 30 days following the last administration of study drug.

The primary change occurs in Section 10.3 Monitoring of Adverse Events and Period of Observation:

Added text: Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug 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 Millennium Department of Pharmacovigilance or designee. SAEs 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).

Rationale for Change:

The addition of the + 10-day window to the Study Procedures section and the Schedules of Events was made for consistency throughout the protocol.

The following sections also contain this change:

- The Schedules of Events for the Single-Agent Arm, Cycle 1.
- The Schedules of Events for the Combination Arm, Cycle 1.
- The Schedules of Events for the Single-Agent Arm, Cycle 2 and Beyond.
- The Schedules of Events for the Combination Arm, Cycle 2 and Beyond.

Change 6: Update the designation for the entity for SAE reporting.

The primary change occurs in Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Initial wording:	**SAE Reporting Contact Information** **Bell Medical Solutions, Inc** Korea: 00798-8171773 Taiwan: 00801-814742 Japan: 0120-490-849
Now reads:	**SAE Reporting Contact Information** ~~**Bell Medical Solutions, Inc**~~ **BI Medical, Inc** Korea: 00798-8171773 Taiwan: 00801-814742 Japan: 0120-490-849

Rationale for Change:

This is an administrative change made to update the name of the entity used for SAE reporting.

The following sections also contain this change:

- The Schedules of Events for the Single-Agent Arm, Cycle 1, footnote o.
- The Schedules of Events for the Single-Agent Arm, Cycle 2 and Beyond, footnote j.
- The Schedules of Events for the Combination Arm, Cycle 1, footnote q.
- The Schedules of Events for the Combination Arm, Cycle 2 and Beyond, footnote o.

Change 7: [redacted] be collected at Screening within 28 days before the first dose of study drug.

The primary change occurs in Section 7.4.20 Bone Marrow Aspirate and Biopsy Collection for Disease Assessment and Molecular Analyses:

Added text: A bone marrow biopsy (in addition to bone marrow aspirate) is required only at Screening to confirm diagnosis; for all other time points, only bone marrow aspirate will be collected unless major changes in the patient's underlying hematological disease are suspected. 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. **Historical results of from up to 2 months prior to enrollment are acceptable for disease classification, but not disease status. If historical results do not show either t(15;17) or t(9;22), then these results can be used to ensure eligibility, provided a formal confirmatory report is sent as soon as it becomes available.**

Bone marrow aspirate collection at Screening is required for study entry

to assess disease burden, cytogenetics, and karyotype. Bone marrow aspirates will also be collected at the end of Cycle 2 and Cycle 4 (Day 21 [6 days] for the Single-Agent Arm and any time between Days 20 and 28 for the Combination Arm, provided that the disease assessment is available before Day 1 of the following cycle) to assess disease response. After Cycle 4, bone marrow aspirates will be performed after completion of every third cycle (eg, Cycle 7, Cycle 10, etc.), and at the EOS visit for patients who withdraw for reasons other than disease progression. [redacted]

Rationale for Change:

These changes were made allow flexibility in bone marrow aspirations collected at Screening and to lessen the burden of additional bone marrow biopsies for patients.

The following sections also contain this change:

- The Schedules of Events for the Combination Arm, Cycle 1, footnotes t and u.
- The Schedules of Events for the Single-Agent Arm, Cycle 1, footnotes r and s.

Change 8: Clarify that site-generated mutation reports are not required if not performed routinely per country/institutional guidelines..

The primary change occurs in the Schedules of Events Single-Agent Arm, Cycle 1, footnote x:

Added text:	x **If mutation analysis is not performed routinely per country/institutional guidelines, it is not required**

Rationale for Change:

This change was made to allow flexibility with obtaining site-generated mutation reports in regions where these analyses are not routinely performed.

The Schedules of Events for the Combination Arm, Cycle 1, footnote y, also contains this change.

Change 9: Revise the test parameters for urinalysis with microscopic analysis for both study arms to include phosphate, and no longer include bilirubin and glucose.

The primary change occurs in Section 7.4.11 Clinical Laboratory Evaluations:

Initial wording:

Urinalysis

Urine samples for urinalysis will be obtained as specified in the Schedules of Events and more frequently if clinically indicated.

Urinalysis With Microscopic Analysis

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

Amended or new wording:

Urinalysis

Urine samples for urinalysis will be obtained as specified in the Schedules of Events and more frequently if clinically indicated.

Urinalysis With Microscopic Analysis

- Turbidity and color
- pH
- Specific gravity
- Protein
- Ketones
- ~~Bilirubin~~
- Occult blood
- Nitrite
- **Phosphate**
- ~~Glucose~~
- Leukocyte esterase
- Microscopic assessment of leukocytes, erythrocytes, bacteria, casts, and crystals

Rationale for Change:

The urine tests for bilirubin and glucose were no longer considered necessary and were therefore removed. The urine test for phosphate was initially included in the panel of urine safety tests, and when these were removed from the protocol (as of Amendment 03), phosphate was added to the urinalysis tests.

The following sections also contain this change:

- The Schedules of Events for the Combination Arm, Cycle 2 and Beyond, footnote l.
- The Schedules of Events for the Single-Agent Arm, Cycle 1, footnote k.
- The Schedules of Events for the Single-Agent Arm, Cycle 2 and Beyond, footnote i.
- The Schedules of Events for the Combination Arm, Cycle 1, footnote m.

Change 10: Remove urine safety assessments from the clinical laboratory evaluations for both study arms.

The primary change occurs in Section 7.4.11 Clinical Laboratory Evaluations:

Deleted text: ~~Urine samples for safety assessment will be obtained as specified in the Schedules of Events and more frequently if clinically indicated.~~

~~**Urine Safety Assessment**~~

- ~~Albumin~~
- ~~Creatinine~~
- ~~Phosphate~~

Rationale for Change:

Urine safety assessments were removed because these assessments were no longer considered necessary for patients in either treatment arm.

The following sections also contain this change:

- The Schedules of Events for the Combination Arm, Cycle 2 and Beyond, footnote m.
- The Schedules of Events for the Single-Agent Arm, Cycle 2 and Beyond, footnote i.

Change 11: Clarify that in the event of a dose delay, creatinine measurements can be delayed by up to 3 days.

The primary change occurs in the Schedules of Events Single-Agent Arm, Cycle 1, footnote k:

Added text: k The select chemistry panel will include the following: blood urea nitrogen, creatinine, lactate dehydrogenase, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. The select chemistry panel will be collected on Day 2. **In the event of a dose delay, creatinine measurements can be delayed up to 3 days.**

Rationale for Change:

The addition of up to a 3-day window was made to allow flexibility in creatinine measurement.

The following sections also contain this change:

- The Schedules of Events for the Single-Agent Arm, Cycle 2 and Beyond, footnote h.
- The Schedules of Events for the Combination Arm, Cycle 1, footnote l.
- The Schedules of Events for the Combination Arm, Cycle 2 and Beyond, footnote k.

Change 12: Provide a definition of postmenopausal.

The primary change occurs in Section 15.9 Definition of Postmenopausal:

Added text:

15.9 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 (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Rationale for Change:

The addition of the definition of postmenopausal was included for clarity and for consistency with program-wide updates.

Change 13: Clarify the minimum interval between doses of pevonedistat.

The primary change occurs in Section 6.4.1 Criteria for Retreatment and Dose Delays:

Initial wording:

Retreatment Within a Cycle

If dosing of either drug is delayed for safety reasons, retreatment may be resumed upon resolution of the safety condition. For pevonedistat, a minimum of 48 hours between any 2 doses should be maintained. In each cycle, a maximum of 3 doses of pevonedistat and 7 doses azacitidine (as applicable) should not be exceeded.

Amended or new wording:	**Retreatment Within a Cycle** If dosing of either drug is delayed for safety reasons, retreatment may be resumed upon resolution of the safety condition. For pevonedistat, a minimum of ~~48 hours~~ **1 full calendar day** between any 2 doses should be maintained **(eg, Day 1 [Monday] and Day 3 [Wednesday])**. In each cycle, a maximum of 3 doses of pevonedistat and 7 doses azacitidine (as applicable) should not be exceeded.

Rationale for Change:

Text describing the interval between doses of pevonedistat was revised for clarity.

Change 14: Remove the restriction on the timing of platelet transfusions and clarify the timing of transfusions for red blood cells, if necessary, to least 1 day prior to investigational product administration.

The primary change occurs in Section 6.6 Permitted Concomitant Medications and Procedures, Table 6.e:

Description of Change:	Text restricting the timing of platelet transfusions was removed, and text was added to clarify that RBC transfusion should occur at least 1 day prior to investigational product administration.

Amended or new wording:

Table 6.e Permitted Concomitant Medications and Procedures

Therapy	Comment
Antiemetics for azacitidine	May be administered according to institutional guidelines.
Hydroxyurea	Dosing of hydroxyurea may be adjusted to control the level of WBC counts to no lower than 10,000 while on treatment with study drugs. The dosing of hydroxyurea and changes to dosing of hydroxyurea should be recorded. Patients may start or restart treatment with hydroxyurea during the study.
~~Platelet transfusion~~	~~Can be administered at any time except during investigational product administration. Each transfusion episode, including the type of transfusion (platelet), should be recorded.~~
~~Red blood cell~~ **RBC** transfusion	To be considered for all patients with anemia, especially those with hemoglobin values <8 g/dL. **RBC transfusion should occur at least 1 day prior to investigational product administration.**

Rationale for Change:

The update in permitted transfusion procedures was made to provide clarity on the window for transfusion prior to investigational product administration and to eliminate a transfusion procedure for which there was no scientific basis to keep.

Change 15: Clarify that lymphoblasts and myelocytes are included in hematology test measures.

The primary change occurs in Section 7.4.11 Clinical Laboratory Evaluations:

Added text:

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential, including circulating blast count
- **Lymphoblasts**
- **Myelocytes**
- Neutrophils (ANC)
  Note: ANC may be calculated from the leukocyte count with differential count; see Section 15.8.

Rationale for Change:

The addition of lymphoblasts and myelocytes was made for clarity.

Change 16: Clarify the percentage increase of bone marrow and circulating blasts in the progressive disease definition.

The primary change occurs in Section 7.4.19.1 Revised Recommendations of the IWG Response Criteria for AML:

Initial wording:

Definition of Progressive Disease

Because the IWG criteria for AML do not provide a standardized definition for progressive disease (PD) [35], in this protocol, PD is defined as 1 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.

Amended or new wording:

Definition of Progressive Disease

Because the IWG criteria for AML do not provide a standardized definition for progressive disease (PD) [35], in this protocol, PD is defined as 1 of the following:

- >50% increase in bone marrow blasts from Baseline value **(**to ~~>30%~~ **a maximum of 100%** blasts**)**.

- >50% increase in circulating blasts from Baseline value **(**to ~~>30%~~ **a maximum of 100%** 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.

Note: When deciding PD for patients with high blasts at Baseline (eg, >70% blasts), investigators are encouraged to use best medical judgement based on the patient's overall clinical profile and in consideration of local institutional guidelines.

Rationale for Change:

The update in the definition of progressive disease was made to add flexibility for investigators when deciding if a patient has progressive disease.

Change 17: Provide additional information on definition of relapse after clinical response.

The primary change occurs in Section 7.4.19.1 Revised Recommendations of the IWG Response Criteria for AML:

Added text: **Definition of 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.

Rationale for Change:

This change was made to clarify the definition of relapse after complete response.

Change 18: Clarify that for acute myeloid leukemia patients, all complete remission includes both complete remission and complete remission with incomplete count recovery.

The primary change occurs in Section 8.1.6 Efficacy Analysis:

Added text: **For AML patients, all CR includes both CR and CRi.**

Rationale for Change:

This change was made to clarify the definition of clinical response for AML patients.

Change 19: Update the investigator responsibilities for compliance with updated International Council for Harmonisation guidelines.

The primary change occurs in Section 11.1 Good Clinical Practice:

Added text:	**The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure 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.**

Rationale for Change:

Investigator responsibilities were updated to comply with updated changes in ICH guidelines.

Change 20: Allow the use of moderate and strong cytochrome P450 3A inhibitors during treatment Cycle 2 and beyond for all study arms.

The primary change occurs in Section 6.5 Excluded Concomitant Medications and Procedures:

Initial wording:	Medications that are generally excluded but are allowed with certain exceptions listed in Table 6.d.
Amended or new wording:	**The use of moderate and strong CYP3A inhibitors is prohibited for 7 days prior to the first dose of study drug(s) only during treatment Cycle 1 for both study arms. In treatment Cycle 2 and beyond, the use of moderate and strong CYP3A inhibitors is permitted. See Section 15.5 for additional details of specific CYP3A inhibitors.**

Rationale for Change:

Preliminary data from 11 patients who completed protocol-specified dosing and PK evaluations to assess the effect of itraconazole, a strong CYP3A inhibitor, on pevonedistat PK indicated that systemic exposures of pevonedistat following IV administration at 20 mg/m^2 in the presence of itraconazole were similar to systemic exposures in the absence of itraconazole. The data support removing moderate or strong CYP3A inhibitors from the list of prohibited concomitant medications in ongoing and planned pevonedistat clinical studies.

The following sections also contain this change:

- Section 5.2 Exclusion Criteria.
- Table 6.d Concomitant Medications Excluded During the Study.
- Table 6.e Permitted Concomitant Medications and Procedures.
- The Schedules of Events for the Single-Agent Arm, Cycle 1, footnote g.
- The Schedules of Events for the Single-Agent Arm, Cycle 2 and Beyond, footnote f.
- The Schedules of Events for the Combination Arm, Cycle 1, footnote i.
- The Schedules of Events for the Combination Arm, Cycle 2 and Beyond, footnote i.
- Section 15.5 Excluded CYP3A Inhibitors and Inducers.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	26-Jun-2017 16:25 UTC
[redacted]	Clinical Approval	26-Jun-2017 16:31 UTC
[redacted]	Clinical Pharmacology Approval	27-Jun-2017 00:54 UTC
[redacted]	Biostatistics Approval	27-Jun-2017 02:13 UTC