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

NCT Number: NCT02610777

Protocol Approve Date: 27 July 2018

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

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

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

CLINICAL STUDY PROTOCOL PEVONEDISTAT-2001 AMENDMENT 04

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

Protocol Number:	Pevonedistat-2001
Indication:	Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, Low-Blast Acute Myelogenous Leukemia
Phase:	2
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2015-000221-37
Therapeutic Area:	Oncology

Protocol History

Original	25 February 2015
Amendment 01	21 October 2015
Amendment 02	13 September 2016
Amendment 03	17 November 2017
Amendment 04	27 July 2018

Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, Massachusetts 02139 United States
Telephone: +1 (617) 679-7000

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

PPD

Rationale for Amendment 04

This document describes changes in reference to the protocol incorporating Amendment 04. The primary reason for this amendment is to employ overall survival (OS) as the primary endpoint of the study. OS is a clearly defined endpoint that is commonly used in studies with patients with higher-risk myelodysplastic syndrome (HR MDS) or chronic myelomonocytic leukemia (CMML) and low-blast acute myelogenous leukemia (AML). Event-free survival (EFS), the previous primary endpoint of the study, is now a secondary endpoint. These changes affect the objectives and endpoints of the study. The protocol was also amended to clarify definitions of response, duration of the study, and concomitant medication therapy, and to update the metabolism profile of pevonedistat and the statistical analysis plan for the study.

Throughout the protocol where text previously read "HR MDS or CMML patients" and "low-blast AML patients," text now reads "patients with HR MDS or CMML" and "patients with low-blast AML."

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

For specific descriptions of text changes, the rationale for each change, and where the changes are located, see Section 15.13.

Changes in Amendment 04

1. Update the pharmacokinetic profile of pevonedistat and risk assessment for drug-drug interactions.
2. Update the primary objective and endpoint of the study to OS.
3. Update secondary objectives and endpoints of the study, including addition of EFS, and clarify definitions of response to the study treatment in the secondary endpoints.
4. Update exploratory objectives and endpoints. CCI [redacted]
5. Update the percentage of patients with OS events initiating the timing of the OS analysis and duration of the study.
6. Update table for concomitant medications that are excluded while receiving single-agent azacitidine study treatment.

7. Update table for concomitant medications that are excluded while receiving combination treatment pevonedistat + azacitidine.
8. Add section for posttrial access to study medication.
9. Specify changes for determination of sample size to align with new primary endpoint.
10. Clarify definition of safety population for purposes of analysis.
11. Specify changes in general methodology for analysis of efficacy.
12. Specify analyses of primary efficacy endpoint OS.
13. Clarify methodology for analysis of secondary efficacy endpoints, including those that are response-related.
14. Clarify populations for analyses of health-related quality of life.
15. Specify CCI [redacted] will be provided CCI [redacted]
16. Delete the exclusion of CYP3A inhibitors from the concomitant medicines table during administration of pevonedistat therapy.

PROTOCOL SUMMARY

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

Number of Patients: It is expected that approximately 117 patients will be enrolled in this study.

Study Objectives

Primary

- To determine in patients with higher-risk myelodysplastic syndrome (HR MDS) or chronic myelomonocytic leukemia (CMML) and low-blast acute myelogenous leukemia (AML) whether the combination of pevonedistat and azacitidine improves overall survival (OS) when compared with single-agent azacitidine.

Secondary

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

combination of pevonedistat and azacitidine improves time to first CR (CR for HR MDS/CMML and low-blast AML; CR + CRi [composite CR] for low-blast AML), or PR when compared with single-agent azacitidine.

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

Exploratory

CCI

[redacted]

CCI

Overview of Study Design: This study is a multicenter, global, randomized, controlled, open-label, phase 2 clinical study of the combination of pevonedistat and azacitidine versus single-agent azacitidine administered in patients with HR MDS or CMML or low-blast AML who have not previously received a hypomethylating agent.

Once enrolled, patients will be randomized at a 1:1 ratio to receive study drug (either single-agent azacitidine or the combination of pevonedistat and azacitidine) in 28-day treatment cycles. All patients will be stratified into 4 categories: low-blast AML, Revised International Prognostic Scoring System (IPSS-R) risk group of very high, high, or intermediate for MDS/CMML [2]. All patients will receive azacitidine (75 mg/m^2 [intravenous or subcutaneous]) on Days 1 through 5, Day 8, and Day 9. Patients randomized to the combination arm will also receive pevonedistat (20 mg/m^2 via 60-minute infusion) on Days 1, 3, and 5 of each cycle. Dose modifications may be allowed.

Patients, including those who achieve a CR, may receive study treatment until they experience unacceptable toxicity, relapse, transformation to AML, or progressive disease as defined in this study.

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

Patients will attend the End-of-Treatment (EOT) visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner. Patients will enter EFS follow-up (for patients with HR MDS/CMML) or response follow-up (for patients with low-blast AML), with study visits every 3 months, to include physical exam, clinical blood tests, HRQOL assessments, hospitalization assessment, bone marrow aspirate sampling, and disease assessment, if their disease has not transformed from HR MDS or CMML to AML (for patients with HR MDS or CMML) or progressed (for patients with low-blast AML), and they have not started subsequent therapy. Patients will enter OS follow-up (contacted every 3 months to document

subsequent therapies and survival status) when they have confirmed transformation to AML (for patient with HR MDS or CMML) or experienced progressive disease (patients with low-blast AML) or have started subsequent therapy.

Disease response assessments for all HR MDS/CMML patients will be based on the Modified International Working Group (IWG) response criteria for MDS [3]. Disease response assessments for patients with low-blast AML will be based on the Revised Recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [4]. Formal disease assessments for study endpoints will be determined based on local bone marrow aspirate blast counts and transfusions, and central lab data (local lab data may be used for time-sensitive clinical decisions).

Bone marrow samples (biopsy and/or aspirate) will be collected at Screening, during treatment, and during follow-up for blast count evaluation (to inform disease burden assessment). Bone marrow aspirate will also be used to analyze tumor cytogenetics, CCI [redacted] Samples will be collected and analyzed from patients in both treatment arms.

Inpatient hospital admissions related to HR MDS or CMML or low-blast AML, as well as RBC- and platelet-transfusion independence, will be monitored as secondary efficacy endpoints. Treatment-emergent resistance will also be monitored.

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

Adverse events and Eastern Cooperative Oncology Group (ECOG) performance status will be assessed, and ECGs, clinical laboratory values, and vital signs will be obtained, to evaluate the safety and tolerability of the study drug treatments. Patient-reported HRQOL will be evaluated using the EORTC-QLQ-C30 and EQ-5D-5L (all patients) and the QOL-E (American English-speaking US patients only) questionnaires.

Study Population:

Patients may be male or female, and must be 18 years or older.

All patients must have morphologically confirmed diagnosis of MDS or nonproliferative CMML (ie, with WBC <20,000/µL) or low-blast AML based on 1 of the following:

French-American-British (FAB) Classifications [5]:

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

OR

World Health Organization (WHO) Classifications [6]:

- Refractory anemia with excess blasts-1 (RAEB-1 – defined as having 5%-9% myeloblasts in the bone marrow)
- Refractory anemia with excess blasts-2 (RAEB-2 – defined as having 10%-19% myeloblasts in the bone marrow and/or 5%-19% blasts in the blood)

- Chronic Myelomonocytic Leukemia-2 (CMML-2 – defined as having 10%-19% myeloblasts in the bone marrow and/or 5%-19% blasts in the blood
- Chronic Myelomonocytic Leukemia-1 (Although CMML-1 is defined as having <10% myeloblasts in the bone marrow and/or <5% blasts in the blood, these patients may enroll only if bone marrow blasts ≥5%)
- WHO-defined AML with 20%-30% myeloblasts in the bone marrow (defined in this protocol as "Low-Blast AML") and ≤30% myeloblasts in peripheral blood who are deemed by the investigator to be appropriate for azacitidine-based therapy

All patients with MDS or CMML must also have a Prognostic Risk Category, based on the Revised International Prognostic Scoring System (IPSS-R)[2], of:

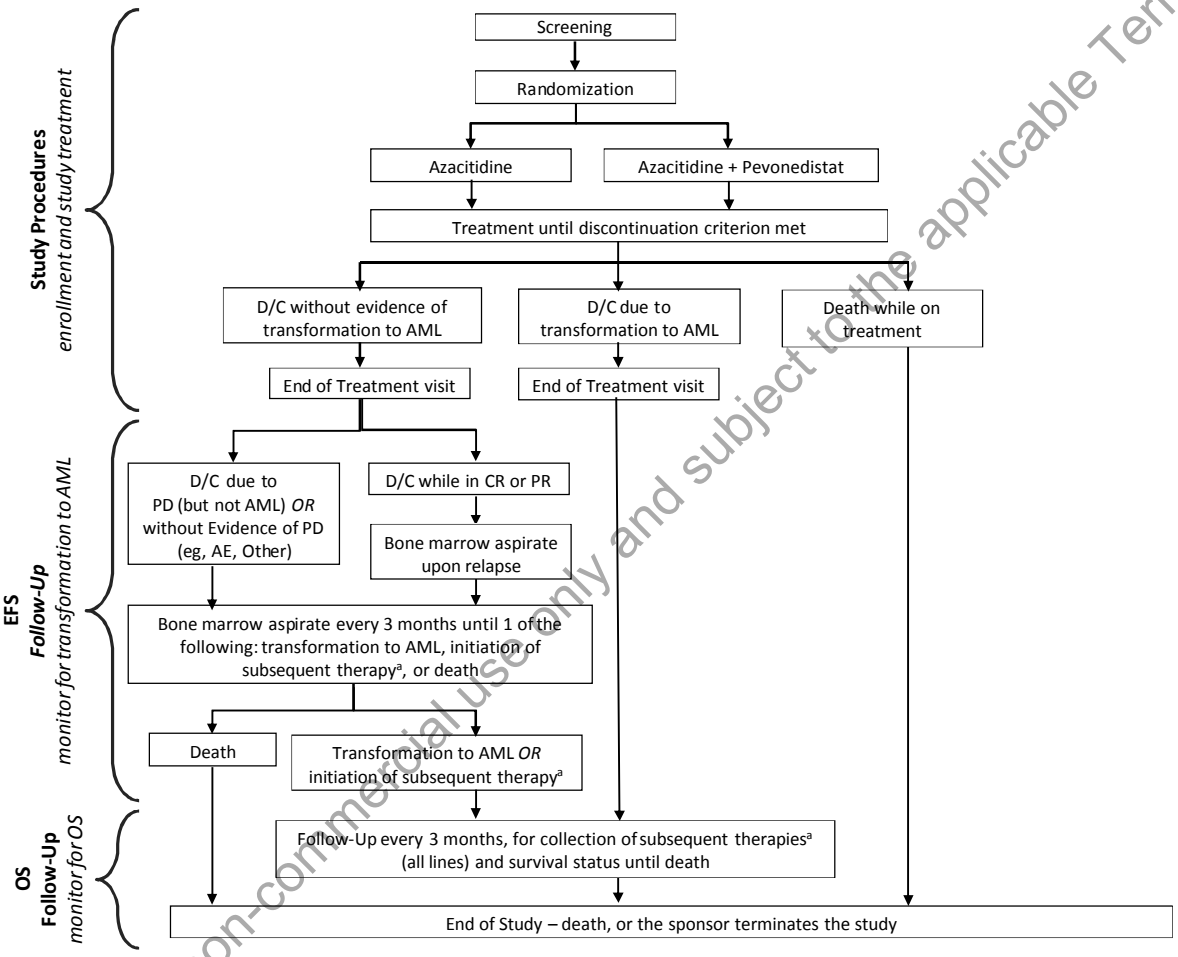
- Very high (>6 points),
- High (>4.5 – 6 points), or
- Intermediate (>3 – 4.5 points): a patient determined to be in the Intermediate Prognostic Risk Category is only allowable in the setting of ≥5% bone marrow myeloblasts.

Complete eligibility details, including additional inclusion and exclusion criteria, are provided in the full protocol.

Duration of Study: Patients will be followed until approximately 60% of patients with HR MDS/CMML have experienced OS events, or termination of the study by the sponsor.

STUDY OVERVIEW DIAGRAM 1:

PATIENTS WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES OR CHRONIC MYELOMONOCYTIC LEUKEMIA



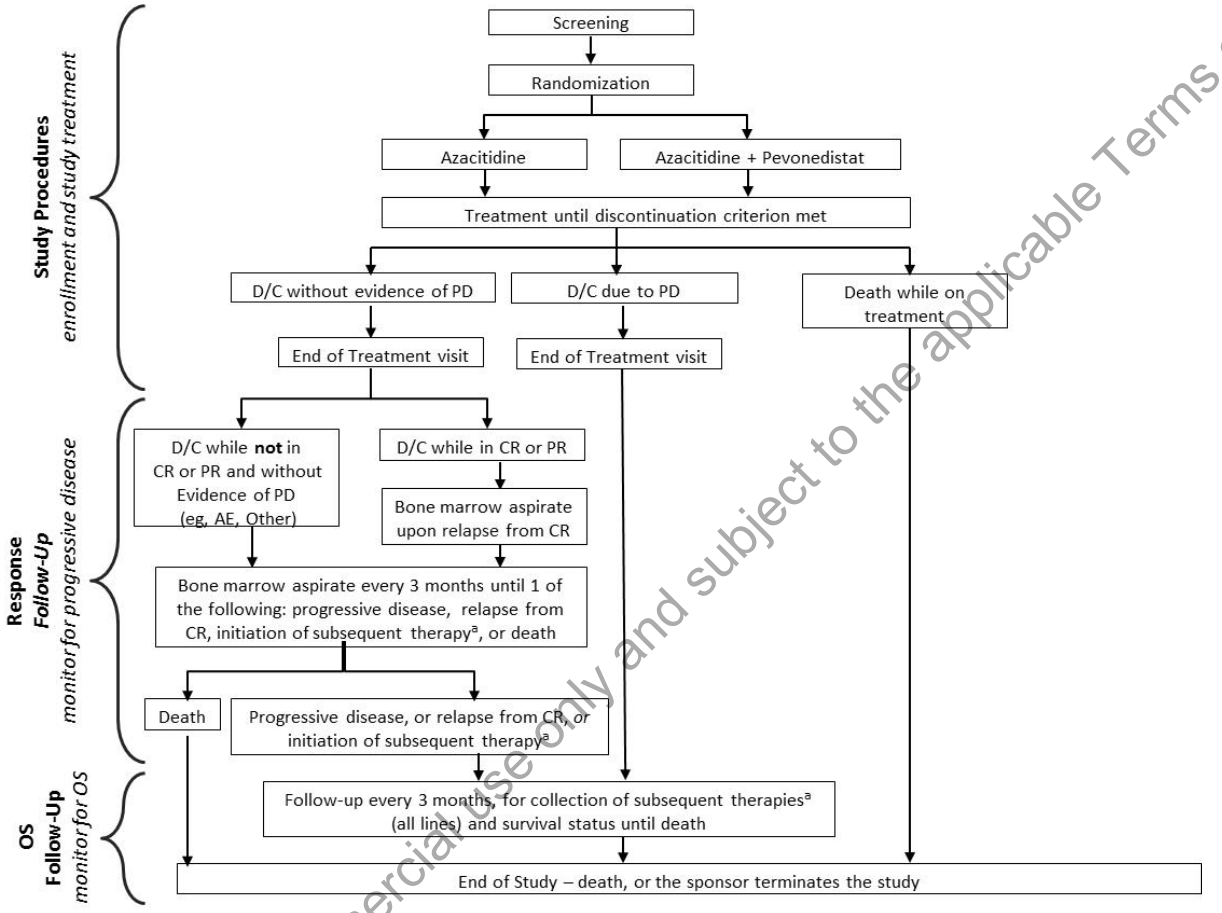
AE=adverse event, AML=acute myelogenous leukemia, CR=complete remission, D/C=discontinuation (of study treatment), EFS=event-free survival, MDS= myelodysplastic syndromes, OS=overall survival, PD=progressive disease, PR=partial remission.

Refer to Section 7.4.21 for response definitions (eg, CR, PR, transformation to AML, PD)

a Subsequent therapy is defined as agent(s) with antileukemic/anti-MDS activity (eg, lenalidomide, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.

STUDY OVERVIEW DIAGRAM 2:

PATIENTS WITH LOW-BLAST ACUTE MYELOGENOUS LEUKEMIA



AE=adverse event, CR=complete remission, D/C=discontinuation (of study treatment), EFS=event-free survival, MDS= myelodysplastic syndromes, OS=overall survival, PD=progressive disease, PR=partial remission.

Refer to Section 7.4.21 for response definitions (eg, CR, PR, PD)

a Subsequent therapy is defined as agent(s) with antileukemic/anti-MDS activity (eg, lenalidomide, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.

SCHEDULE OF EVENTS

	Screening (a,b)	Treatment Cycle (28 Days) (c,d,e)											Follow-up		
		Cycle 1							Cycle 2 and beyond				EFS (HR MDS/ CMML)	Response (AML)	OS
	Days	1	2	3	5	8	15	21	1	3	5	EOT (f)	Every 3 months	Every 3 months	Every 3 months
Procedures	**Window**						±1 day	±1 day				+10 days	±2 weeks	±2 weeks	±2 weeks
Informed consent	X														
Inclusion/Exclusion (g)	X														
Demographics	X														
Complete medical history and IPSS-R risk categorization (patients with HR MDS, CMML)	X														
Modified Charlson comorbidity index assessment (h)	X														
Complete physical examination	X											X			
Symptom-directed physical examination		X							X				X	X	
Height	X														
Weight	X	X(i)							X(i)			X			
ECOG performance status	X								X			X			
Vital signs (j)	X	X		X	X				X	X	X	X			
12-lead ECG (k)	X											X			
Chest X-ray (l)	X														
Pregnancy test (m)	X	X							X			X			
Hematology (n)	X	X		X	X	X	X	X	X			X	X	X	
Coagulation (o)	X														
Complete chemistry panel (n,p)	X								X			X	X	X	
Select chemistry panel (n,q)		X		X	X	X	X	X		X	X				
Blood phosphate (r)					X						X				
Reticulocyte count and ferritin (s)	X	X							X			X			

	Screening (a,b)	Treatment Cycle (28 Days) (c,d,e)											Follow-up		
		Cycle 1							Cycle 2 and beyond				EFS (HR MDS/ CMML)	Response (AML)	OS
	Days	1	2	3	5	8	15	21	1	3	5	EOT (f)	Every 3 months	Every 3 months	Every 3 months
Procedures	**Window**						**±1 day**	**±1 day**				**+10 days**	**±2 weeks**	**±2 weeks**	**±2 weeks**
Urinalysis with microscopic analysis (t)	X											X			
EORTC-QLQ-C30 (u)	X	X							X			X	X	X	
QOL-E (u)	X	X							X			X	X	X	
EQ-5D-5L (u)	X	X							X			X	X	X	
Hospitalization assessment (u)		X							X			X	X	X	
Blood samples for PK		X (v)		X (v)	X (v)				X (w)						
Bone marrow aspiration/biopsy and investigator disease assessment	See the Bone Marrow Collection and Assessment Schedule														
CCI [redacted]															
Buccal swab for germline DNA analysis/DME genotyping	X (x)														
SAE collection (y)	SAEs including serious pretreatment events will be reported from the time informed consent is signed through 30 days after the last dose of any study drug														
AE collection	Recorded from the first dose of any study drug through 30 days after the last dose of any study drug														
Concomitant medications/therapy	Recorded from the first dose of any study drug through 30 days after the last dose of any study drug														
RBC and platelet transfusion documentation	Recorded from 8 weeks before randomization through 30 days after the last dose of any study drug														
Subsequent therapies (z)												X	X	X	X
Survival follow-up contact															X
Study Drug Administration: Single-Agent Azacitidine or Combination Pevonedistat Plus Azacitidine (e,zz,zzz)															
Pevonedistat infusion		Days 1, 3, and 5 of each cycle													
Azacitidine administration		Days 1-5 and 8 and 9 of each cycle													

AE=adverse event, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AML=acute myelogenous leukemia, aPTT=activated partial thromboplastin time, AST=aspartate

	Screening (a,b)	Treatment Cycle (28 Days) (c,d,e)											Follow-up		
		Cycle 1							Cycle 2 and beyond				EFS (HR MDS/ CMML)	Response (AML)	OS
	Days	1	2	3	5	8	15	21	1	3	5	EOT (f)	Every 3 months	Every 3 months	Every 3 months
Procedures	**Window**						±1 day	±1 day				+10 days	±2 weeks	±2 weeks	±2 weeks

aminotransferase, BSA=body surface area, BUN=blood urea nitrogen, CMML=chronic myelomonocytic leukemia, DME=drug metabolizing enzymes, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EFS=event-free survival, EOT=end of treatment, HRQOL=health-related quality of life, IPSS-R=Revised International Prognostic Scoring System, IV=intravenous(ly), LDH=lactate dehydrogenase, MDS=myelodysplastic syndromes, OS=overall survival, PK=pharmacokinetic, PT=prothrombin time, RBC=red blood cell, SAE=serious adverse event, SC=subcutaneous(ly), WBC=white blood cell.

(a) Screening assessments will be performed within 28 days before randomization. Baseline assessments are defined as those performed at the closest time before the start of study drug administration.

(b) Except for hematology, 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 the previous Friday.

(c) On dosing days, all procedures are to be performed prior to pevonedistat or azacitidine dosing unless specified otherwise.

(d) For a new cycle of treatment with study drug(s) to begin, toxicities considered to be related to treatment with study drug(s) must have resolved to the level or grade defined in Section 6.3.1.

(e) The first dose of study drug must be administered within 5 days of randomization on study. It is strongly recommended that dosing for both treatment arms occur on the days specified. However, dosing of either drug may be delayed for safety reasons or other unavoidable circumstances (eg, weather conditions affecting clinic accessibility). If pevonedistat dosing is delayed, a minimum of 1 full calendar day 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. For the combination arm, pevonedistat and azacitidine should always be administered on the same day (eg, instead of pevonedistat dosing on Days 1, 3, and 5, it would be acceptable to dose on Days 1, 5, and 8). If dosing is adjusted, study procedures should be performed on the actual day of dosing.

(f) The EOT visit will occur 30 days (+10 days) after the last dose of study drug(s) or before the start of subsequent antineoplastic therapy if that occurs sooner. After the EOT visit, patients will enter EFS follow-up if their disease has not transformed to AML (for patients with HR MDS or CMML) or enter response follow-up if their disease has not progressed (for patients with low-blast AML) (as defined in Section 7.4.21), and they have not started subsequent therapy. Patients will enter OS follow-up when they have confirmed transformation to AML (for patients with HR MDS or CMML at study entry), experienced progressive disease (for patients with low-blast AML at study entry), or have started subsequent therapy.

(g) Confirmation of patient eligibility by the sponsor's project clinician (or designee) is required prior to randomization. A Patient Eligibility Checklist must be completed and submitted by the investigator for review and approval by the sponsor or designee prior to patient randomization.

(h) See Section 15.7 for the modified Charlson comorbidity index.

(i) Weight will be measured within 3 days before Day 1 dosing in each cycle, for calculating BSA. BSA will be calculated using a standard formula (see example in Section 15.8) 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.

(j) Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected at Screening, predose on Days 1, 3, and 5 on each treatment arm of each treatment cycle, at EOT, and as clinically indicated. Vital sign measurements will be taken with the patient in the supine or sitting position.

(k) Additional ECGs may be performed as clinically indicated.

(l) If a chest X-ray or chest CT scan was performed within 2 months prior to randomization, the chest X-ray does not need to be performed during Screening.

(m) A serum pregnancy test will be performed for women of childbearing potential at Screening. A pregnancy test must also be performed for women of childbearing potential at

	Screening (a,b)	Treatment Cycle (28 Days) (c,d,e)											Follow-up		
		Cycle 1							Cycle 2 and beyond				EFS (HR MDS/ CMML)	Response (AML)	OS
	Days	1	2	3	5	8	15	21	1	3	5	EOT (f)	Every 3 months	Every 3 months	Every 3 months
Procedures	Window						±1 day	±1 day				+10 days	±2 weeks	±2 weeks	±2 weeks

every cycle (typically performed on Day 1 of the cycle; however, if a serum pregnancy test is used, this may be performed up to 3 days before Day 1) with negative results available before the first dose is administered in that cycle. A pregnancy test will also be performed for women of childbearing potential at the EOT visit. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

(n) Clinical laboratory evaluations will be performed by a central laboratory. The central laboratory results also should be used for determination of eligibility by the sponsor's project clinician (or designee) prior to randomization. For dosing decisions and/or safety concerns, local hematology and chemistry results should be used; however, samples must still be sent to the central lab as well. Hematology and chemistry samples may be collected up to 3 days before Day 1 dosing and 24 hours before Days 3 and 5 dosing, when required. Local laboratory evaluations may be done more frequently at the investigator's discretion.

(o) Coagulation panel includes PT and aPTT (to be performed by the central laboratory).

(p) The complete chemistry panel will include the following: BUN, creatinine, sodium, potassium, chloride, carbon dioxide, glucose, urate, total bilirubin, direct bilirubin, ALP, LDH, AST, ALT, albumin, magnesium, phosphate, and calcium.

(q) The select chemistry panel will include the following: BUN, creatinine, total bilirubin, ALP, AST, and ALT.

(r) Blood phosphate test to be performed on Day 5 of each treatment cycle or the day on which the third dose of pevonedistat is given if it is not Day 5 (to be performed by the central laboratory).

(s) Reticulocyte counts and ferritin level testing will be performed by the central laboratory only. Reticulocyte count and ferritin samples may be collected up to 3 days before Day 1 dosing.

(t) Urinalysis will include assessments of turbidity and color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, glucose, and leukocyte esterase. Urine microscopic analysis will include erythrocytes, leukocytes, bacteria, casts, and crystals. These samples will be analyzed by a central laboratory.

(u) Patient-reported outcomes (HRQOL) and hospitalization assessment (ie, details regarding any hospitalizations since the last assessment) should be completed before any other study procedures are performed or study drug regimen is administered. The EORTC-QLQ-C30 and EQ-5D-5L will be completed for all patients, and the QOL-E will be completed for American English-speaking US patients only.

(v) Combination Pevonedistat Plus Azacitidine Arm only: blood samples (approximately 3 mL each) for the determination of pevonedistat plasma concentrations will be collected during Cycle 1 at the following time points: Day 1 at the end of the pevonedistat infusion (immediately before stopping the infusion), at 1.5 hours (±30 minutes) and at 4 hours (± 45 minutes) after completion of the pevonedistat infusion; Day 3 predose (within 10 minutes before azacitidine dosing); and Day 5 predose (within 10 minutes before azacitidine dosing), at the end of the pevonedistat infusion (immediately before stopping the infusion), and prior to the patient's discharge from the clinic visit. The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, and particular care should be given to the recording of blood sampling times that occur close to the infusion. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

(w) Combination Pevonedistat Plus Azacitidine Arm only: blood samples (approximately 3 mL each) for the determination of pevonedistat plasma concentrations will be collected at Cycle 2 and Cycle 4 Day 1 (at the end of the pevonedistat infusion [immediately before stopping the infusion] and 3 hours [± 45 minutes] after completion of the pevonedistat infusion); an additional sample will be collected predose (within 10 minutes before azacitidine dosing) on Cycle 4 Day 3. The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, and particular care should be given to the recording of blood sampling times that occur close to the infusion. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

(x) CCI [redacted].

	Screening (a,b)	Treatment Cycle (28 Days) (c,d,e)											Follow-up		
		Cycle 1							Cycle 2 and beyond				EFS (HR MDS/ CMML)	Response (AML)	OS
	Days	1	2	3	5	8	15	21	1	3	5	EOT (f)	Every 3 months	Every 3 months	Every 3 months
Procedures	Window						±1 day	±1 day				+10 days	±2 weeks	±2 weeks	±2 weeks

(y) SAEs will be entered on the eCRF and also reported to CCI (see Section 10.2). Serious pretreatment events (occurring before the first dose of any study drug) will only be reported to CCI 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).

(z) Subsequent therapy is defined as an agent(s) with antileukemic/anti-MDS activity (eg, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.

(zz) Combination Pevonedistat Plus Azacitidine Arm only: See Section 6.1.2 for pevonedistat dosing instructions. On Days 1, 3, and 5 when both study drugs are administered, azacitidine will be administered first followed by pevonedistat. Subsequent pevonedistat doses may be reduced due to toxicity in accordance with Section 6.3.

(zzz) All patients will receive azacitidine 75 mg/m^2 IV or SC on Days 1 through 5 (inclusive), Day 8, and Day 9 of each cycle in accordance with Section 6.1.1. The azacitidine dose may be reduced due to toxicity in accordance with Section 6.3.

Bone Marrow Collection and Assessment Schedule

Assessment	Screening	Cycle 2 Day 22 (+6 Days)	Cycle 4 Day 22 (+6 days)	Cycle 7 Day 22 (+6 days)	Cycle 10 Day 22 (+6 days), and Then Every 3 Cycles Thereafter	Relapse	EFS/Response Follow-up (Every 3 Months)
Bone marrow blast count *(Local and central analyses)*	X (a)	X (b)	X (b,c)	X (b,c)	X (b,c)	X	X (c)
Cytogenetics (d) *(Local analysis only)*	X	X	X (c)	X (c)	X (c)	X	
Mutation analysis (e) *(Local analysis only)*	X						
Molecular analysis *(Central analysis only)*	X(f)	X(f)	X(g)	X(g)		X (h)	

CR=complete remission, EFS=event-free survival, FISH=fluorescence in situ hybridization, PCR=polymerase chain reaction, PD=progressive disease.

(a) A bone marrow biopsy (in addition to bone marrow aspirate) is required only at Screening to confirm the diagnosis; bone marrow aspirates will be collected at all other time points, at relapse or PD, and as clinically indicated (see Section 7.4.20 for detailed examples). However, a bone marrow biopsy may be collected with bone marrow aspirate in accordance with institutional guidelines. If a bone marrow aspirate and biopsy were performed within 28 days prior to randomization, these archival samples may be used to confirm diagnosis and do not need to be repeated. However, a bone marrow aspirate for molecular analysis is still required at Screening (see footnote (f) below). The bone marrow pathology report(s) will be submitted to the central laboratory. If a bone marrow biopsy is not collected routinely per country institutional guidelines, it is not required.

(b) A bone marrow aspirate for blast count (to inform disease burden assessment) will be performed on Day 22 (+6 days) of Cycle 2, Cycle 4, and every 3 cycles thereafter (Cycle 7, Cycle 10, etc.). Results must be available before dosing starts in the next cycle.

(c) Following Cycle 4, bone marrow aspirates will be performed only as clinically indicated in patients who achieve CR. In all other patients who do not achieve CR, bone marrow assessments will be performed after completion of every third treatment cycle. Additional bone marrow aspirates may be performed if warranted by changes in peripheral blood counts.

(d) Cytogenetics analysis will be done locally at the clinical site: a bone marrow aspirate sample will be tested according to institutional guidelines in a cytogenetics laboratory routinely used by the site. Analyses should be done by karyotype, and by FISH if possible. Results will be collected in the eCRF and the cytogenetics report(s) will be submitted to the central laboratory.

(e) Mutation analysis to be performed locally at the clinical site according to institutional guidelines/standard practice (eg, genomic analysis or PCR analysis) and this information will be collected from sites. If mutation analysis is not performed routinely per country/institutional guidelines, it is not required. Results will be collected in the eCRF and the mutation analysis report(s) will be submitted to the central laboratory.

(f) A fresh bone marrow aspirate obtained at screening, any time prior to the first administration of study drug, will be used for baseline molecular characterization. A bone marrow aspirate sample for molecular analysis will also be obtained on Day 22 (+6 days) of Cycle 2. Bone marrow aspirate samples will be sent to a central laboratory for molecular analysis.

(g) A bone marrow aspirate sample for molecular analysis will be obtained on Day 22 (+6 days) of Cycle 4. A bone marrow aspirate sample for molecular analysis will also be obtained Day 22 (+6 days) of Cycle 7 for patients who do not have a confirmed CR at Cycle 4. Bone marrow aspirate samples will be sent to a central laboratory for molecular analysis.

(h) If relapse is suspected, the sample for molecular analysis will be collected at the time the bone marrow sample for disease assessment is collected and sent to the central laboratory (per instructions in the Laboratory Manual).

TABLE OF CONTENTS

LIST OF TABLES 20
LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS 21
1. BACKGROUND AND STUDY RATIONALE 25
1.1 Scientific Background 25
1.1.1 Diseases Under Treatment 25
1.1.2 Study Drug: Pevonedistat 28
1.2 Nonclinical Experience 28
1.2.1 Single-Agent Pevonedistat 28
1.2.2 Pevonedistat With Azacitidine 29
1.3 Clinical Experience 30
1.4 Pharmacokinetics of Pevonedistat 32
1.4.1 Nonclinical Pharmacokinetics and Risk Assessment for Drug-Drug Interactions 32
1.4.2 Clinical Pharmacokinetics 33
1.5 Study Rationale 34
1.5.1 Rationale for Study Population 34
1.5.2 Rationale for the Combination of Pevonedistat Plus Azacitidine 35
1.5.3 Rationale for Dose and Schedule of Study Drugs 35
1.5.4 Rationale for Molecular Analyses 36
1.5.5 Rationale for Health-Related Quality of Life Assessments 40
1.6 Potential Risks and Benefits 41
1.6.1 Azacitidine 41
1.6.2 Pevonedistat Plus Azacitidine 42
1.6.3 Potential for Drug-Drug Interactions 44
2. STUDY OBJECTIVES 45
2.1 Primary Objective 45
2.2 Secondary Objectives 45
2.3 Exploratory Objectives 47
3. STUDY ENDPOINTS 48
3.1 Primary Endpoint 48
3.2 Secondary Endpoints 48
3.3 Exploratory Endpoints 49
4. STUDY DESIGN 50
4.1 Overview of Study Design 50
4.2 Number of Patients 53
4.3 Duration of Study 53
5. STUDY POPULATION 54
5.1 Inclusion Criteria 54
5.2 Exclusion Criteria 57
6. STUDY DRUG 59
6.1 Study Drug Administration 59
6.1.1 All Patients – Azacitidine Dosing 59
6.1.2 Additional Instructions for the Combination Arm – Pevonedistat Plus Azacitidine Dosing 59
6.2 Reference/Control Therapy: Azacitidine 60

6.3 Dose Modification Guidelines 61
6.3.1 Criteria for Retreatment and Dose Delays 61
6.3.2 Dose Modification for Hematologic Toxicities 62
6.3.3 Dose Modification for Nonhematologic Toxicities 64
6.4 Excluded Concomitant Medications and Procedures 65
6.5 Permitted Concomitant Medications and Procedures 66
6.6 Precautions and Restrictions 67
6.7 Management of Clinical Events 68
6.7.1 Azacitidine 68
6.7.2 Combination Pevonedistat Plus Azacitidine 69
6.8 Blinding and Unblinding 70
6.9 Description of Investigational Agents 70
6.9.1 Azacitidine 70
6.9.2 Pevonedistat 70
6.10 Preparation, Reconstitution, and Dispensation 71
6.11 Packaging and Labeling 71
6.12 Storage, Handling, and Accountability 72
7. STUDY CONDUCT 72
7.1 Study Personnel and Organizations 72
7.2 Arrangements for Recruitment of Patients 72
7.3 Treatment Group Assignments 73
7.4 Study Procedures 73
7.4.1 Informed Consent 73
7.4.2 Inclusion/Exclusion Confirmation 74
7.4.3 Patient Demographics 74
7.4.4 Medical History and IPSS-R Risk Categorization 74
7.4.5 Modified Charlson Comorbidity Index Assessment 76
7.4.6 Physical Examination 76
7.4.7 Patient Height 76
7.4.8 Patient Weight 76
7.4.9 Eastern Cooperative Oncology Group Performance Status 76
7.4.10 Vital Signs 77
7.4.11 Electrocardiogram 77
7.4.12 Chest X-ray 77
7.4.13 Enrollment 77
7.4.14 Clinical Laboratory Evaluations 77
7.4.15 Pregnancy Test 79
7.4.16 Health-Related Quality of Life Questionnaires 79
7.4.17 Hospitalization Assessment 81
7.4.18 Pharmacokinetic Measurements 81
7.4.19 CCI
7.4.20 Bone Marrow Aspirate and Biopsy Collection and Analysis 82
7.4.21 Disease Assessment 85
7.4.22 Adverse Events 90
7.4.23 Concomitant Medications and Procedures 90
7.5 Completion of Treatment 91

7.6 Completion of Study 92
7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement 92
7.8 Withdrawal of Patients From Study 93
7.9 Study Compliance 93
7.10 Posttreatment Follow-up Assessments (Event-Free Survival, Response Follow-up, and Overall Survival) 94
7.11 Posttrial Access 94
7.11.1 Posttrial Access 94
7.11.2 Duration of PTA 94
8. STATISTICAL AND QUANTITATIVE ANALYSES 95
8.1 Statistical Methods 95
8.1.1 Determination of Sample Size 95
8.1.2 Randomization and Stratification 95
8.1.3 Populations for Analysis 95
8.1.4 Procedures for Handling Missing, Unused, and Spurious Data 96
8.1.5 Demographic and Baseline Characteristics 96
8.1.6 Efficacy Analysis 96
8.1.7 Analyses of Health-related Quality of Life 101
8.1.8 Pharmacokinetics/Pharmacodynamics/CCI 101
8.1.9 Safety Analysis 102
8.1.10 Interim Analysis 104
9. STUDY COMMITTEES 104
9.1 Millennium Safety Monitoring 104
9.2 Independent Data Monitoring Committee 105
10. ADVERSE EVENTS 105
10.1 Definitions 105
10.1.1 Pretreatment Event Definition 105
10.1.2 Adverse Event Definition 105
10.1.3 Serious Adverse Event Definition 105
10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events 107
10.3 Monitoring of Adverse Events and Period of Observation 108
10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events 108
10.5 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities 109
11. ADMINISTRATIVE REQUIREMENTS 109
11.1 Good Clinical Practice 109
11.2 Data Quality Assurance 109
11.3 Electronic Case Report Form Completion 110
11.4 Study Monitoring 110
11.5 Ethical Considerations 111
11.6 Patient Information and Informed Consent 111
11.7 Patient Confidentiality 111
11.8 Investigator Compliance 111
11.9 On-site Audits 112
11.10 Investigator and Site Responsibility for Drug Accountability 112
11.11 Product Complaints 112

11.12 Closure of the Study 113
11.13 Record Retention 114
12. USE OF INFORMATION 114
13. INVESTIGATOR AGREEMENT 115
14. REFERENCES 116
15. APPENDICES 122
15.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status 122
15.2 Cockcroft-Gault Equation 122
15.3 Definition of Postmenopausal 122
15.4 Methods of Contraception Considered to be Effective 123
15.5 New York Heart Association Classification of Cardiac Disease 125
15.6 Excluded CYP3A Inducers 125
15.7 Modified Charlson Comorbidity Index 126
15.8 Body Surface Area Calculation 126
15.9 Formula for Absolute Neutrophil Count Calculation 126
15.10 Amendment 01 Rationale and Purposes 128
15.11 Amendment 02 Rationale and Purposes 132
15.12 Amendment 03 Rationale and Purposes 136
15.13 Amendment 04 Detailed Description of Amendments to Text 137

LIST OF TABLES

Table 6.a Concomitant Medications Excluded While Receiving Study Treatment: Single-Agent Azacitidine Arm 65
Table 6.b Concomitant Medications Excluded While Receiving Study Treatment: Combination Pevonedistat Plus Azacitidine Arm 66
Table 6.c Concomitant Medications and Procedures Permitted During the Study 66
Table 7.a IPSS-R Prognostic Score Values 75
Table 7.b IPSS-R Cytogenetic Risk Groups 75
Table 7.c IPSS-R Prognostic Risk Categories/Scores 76
Table 7.d Response Criteria for Altering Natural History of MDS and CMML 87
Table 7.e Response Criteria for Hematologic Improvement for MDS and CMML 89
Table 7.f Response Criteria for AML 89
Table 15.a In Vivo Inducers of CYP3A 125
Table 15.b Modified Charlson Comorbidity Index 126

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCRP	breast cancer resistance protein
BSA	body surface area
BUN	blood urea nitrogen
CCR	conventional care regimen
CDL	cullin-dependent ubiquitin E3 ligase
Cdt-1	chromatin-licensing and DNA-replication factor-1
CI	confidence interval
C_{max}	maximum (peak) concentration
CMH	Cochran-Mantel-Haenszel
CMML	chronic myelomonocytic leukemia
CO_2	carbon dioxide
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CT	computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DME	drug metabolizing enzyme
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival

Abbreviation	Term
EQ-5D-5L	EuroQoL 5 dimensions 5 levels (a quality of life questionnaire of the "EuroQoL Group Association" that was expanded to a 5-level instrument)
EORTC-QLQ-C30	European Organisation for the Research and Treatment of Cancer Core Quality of Life Questionnaire
EOT	end of treatment
FAB	French-American-British
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage colony-stimulating factor
hERG	human ether-à-go-go related gene
HI	hematologic improvement
HIV	human immunodeficiency virus
HLT	high-level term
HR MDS	higher-risk MDS
HRQOL	health-related quality of life
IB	Investigator's Brochure
IC_{50}	concentrations producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IWG	International Working Group
IWRS	interactive web response system
LDH	lactate dehydrogenase
LFT	liver function test
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and its affiliates

Abbreviation	Term
miRNAs	micro-RNAs
MLN4924	research name of pevonedistat hydrochloride; TAK-924
MRD	measurable residual disease
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEDD8	neural precursor cell expressed developmentally down-regulated protein 8
NGS	next-generation sequencing
Nrf2	NFE2-related factor 2
NYHA	New York Heart Association
OATP	organic anion-transporting polypeptides
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease, disease progression
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial remission
PRO	patient-reported outcome
PT	preferred term
PT	prothrombin time
PTA	posttrial access
QALYs	quality-adjusted life years
QOL-E	Quality of Life in Hematological patients (myelodysplastic syndromes) (questionnaire from the Associazione QOL-ONE)
RAEB	refractory anemia with excess blasts
RAEB-t	refractory anemia with excess blasts in transformation
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SmPC	Summary of Product Characteristics
SOC	system organ class
SUSAR	suspected unexpected adverse reaction
$t_{1/2}$	terminal disposition half-life

Abbreviation	Term
TEAE	treatment-emergent adverse event
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia
USPI	United States prescribing information
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Diseases Under Treatment

Myelodysplastic syndromes (MDS) are a group of biologically and clinically heterogeneous hematopoietic disorders derived from an abnormal multipotent progenitor cell. The diagnosis of MDS is made based upon findings in the peripheral blood and bone marrow as interpreted within the clinical context. Most cases of MDS are diagnosed based upon the presence of 3 main features:

- Otherwise unexplained quantitative changes in 1 or more of the blood and bone marrow elements (ie, red cells, granulocytes, platelets).
- Morphologic evidence of significant dysplasia (ie, ≥10 percent of erythroid precursors, granulocytes, or megakaryocytes) upon visual inspection of the peripheral blood smear, bone marrow aspirate, and bone marrow biopsy in the absence of other causes of dysplasia.
- Blast forms account for less than 20 percent of the total cells of the bone marrow aspirate and peripheral blood. Cases with higher blast percentages are considered to have acute myelogenous leukemia (AML). In addition, the presence of myeloid sarcoma or certain genetic abnormalities, such as those with t(8;21), inv(16), or t(15;17), are considered diagnostic of AML, irrespective of the blast cell count.

MDS are classified using the World Health Organization (WHO) classification system [6,7] based upon a combination of morphology, immunophenotype, genetics, and clinical features. The WHO classification system was built upon the French-American-British (FAB) Cooperative Group classification [5].

MDS are commonly divided into lower- or higher-risk categories based on the Revised International Prognostic Scoring System (IPSS-R) for MDS, which is a scoring system useful for estimating overall survival and the risk of transformation to AML [2]. Overall, approximately 25% of patients with very high, high, or intermediate IPSS-R scores will transform to AML within 0.7 years, 1.4 years, and 3.2 years, respectively [2]. Median survival for patients with MDS varies from years to months and decreases with increasing IPSS-R score.

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 (OS), and decrease progression to AML. Treatment of patients with lower-risk MDS (often defined as patients with <5% myeloblasts and/or normal or good risk cytogenetics and few cytopenias) focuses on minimizing blood product transfusions and maximizing quality of life through use of supportive care (eg, antibiotics as needed for infections, red blood cell transfusions), growth factors such as erythropoiesis stimulating factors or immunosuppressive drugs. Treatment for patients with higher-risk disease often includes DNA hypomethylating agents (azacitidine and decitabine) [8]. Rarely, intensive chemotherapy is used in patients with higher-risk MDS (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) [9-11].

Hypomethylating agents produce objective hematologic responses in approximately half of patients with MDS, delay leukemic progression, improve quality of life, and, for azacitidine only, prolong survival in patients with HR MDS. Nevertheless, treatment with hypomethylating agents is not curative, and most patients relapse within 2 years. Lenalidomide, an immunomodulatory thalidomide congener, significantly improves red blood cell transfusion-independence rates and increases hemoglobin, but it is approved only for use in patients with the 5q syndrome subtype of low-risk MDS [9,10,12-14].

The only known curative therapy for MDS is allogeneic 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 [15]. 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) [10,16,17]. More recent therapeutic approaches to patients with MDS with higher-risk disease have involved combining drugs with hypomethylating agents, either to take advantage of synergistic properties of, for example, histone deacetylase inhibition combined with epigenetic modification, or to capitalize on non-overlapping mechanisms of action [18,19].

As detailed by Zandberg et al, 2013 [20], chronic myelomonocytic leukemia (CMML) is a clonal stem cell disorder that displays features of both MDS and a myeloproliferative

neoplasm. Diagnostic criteria for CMML include persistent peripheral blood monocytosis (>$10x10^9$/L), absence of the Philadelphia chromosome and/or BCR-ABL1 fusion gene, absence of platelet-derived growth factor receptor or gene rearrangement, fewer than 20% blasts in the blood and the bone marrow, and dysplasia of 1 or more myeloid lineages [21]. CMML was classified as an MDS in the FAB classification system in 1982 [5], but was subsequently reclassified as a mixed myelodysplastic/myeloproliferative disorder by the WHO classification system in 2001 [22]. CMML shares clinical and biological features with MDS, including development of cytopenias and bone marrow failure, risk of progression to AML, and overlapping recurring cytogenetic abnormalities. Like MDS, it has a variable clinical course, with reported rates of transformation to AML of 15% to 52% and a median OS of 12 to 18 months [23-25]. Treatment modalities for the 2 diseases are also similar, including hematopoietic growth factors (erythropoiesis-stimulating agents and granulocyte colony-stimulating factor), transfusion support, hypomethylating agents, and allogeneic hematopoietic stem cell transplantation.

Prognostic scoring systems for MDS, including the IPSS-R scoring system used in this study, have been routinely applied to patients with CMML and have been shown to be predictive of both transformation to AML and overall survival [26].

Low marrow blast count (20%-30%) WHO-defined AML was previously classified as refractory anemia with excess blasts in transformation (RAEB-t). WHO criteria now define AML as > 20% bone marrow blasts. In a phase 3 randomized trial, azacitidine significantly prolonged overall survival compared with conventional care regimens (CCRs) in patients with higher risk MDS [13]. A subgroup analysis of 113 elderly patients (median age, 70 years) compared the effects of azacitidine versus CCRs on overall survival of these FAB-defined RAEB-t and WHO-defined AML [13]. Median overall survival for azacitidine-treated patients was 24.5 months compared with 16.0 months for CCR-treated patients (hazard ratio=0.47). Furthermore, azacitidine was associated with fewer total days in the hospital than CCR. In another phase 3 study, 191 patients with higher-risk MDS by FAB criteria were randomly assigned to azacitidine or best supportive care [27]. Of these, 45 patients had WHO-defined AML. Response rates to azacitidine were similar in MDS and these low marrow blast AML patients. Azacitidine was associated with improvements in physical function, symptoms, and psychological state. Patients assigned to supportive care were permitted to cross over to azacitidine at the time of progression; this design limited survival analysis. Based on these studies, azacitidine-based therapy is a standard of care in low marrow blast count WHO-defined AML.

1.1.2 Study Drug: 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 that is being developed for the treatment of malignancies. NEDD8-activating enzyme (NAE) 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. As detailed in Section 1.5, the nonclinical and preliminary clinical experience in AML with pevonedistat alone or in combination supports further evaluation in the subset of patients who are classified as HR MDS or CMML or low-blast AML.

1.2 Nonclinical Experience

1.2.1 Single-Agent Pevonedistat

Pevonedistat is a potent and selective inhibitor of NAE activity.

Pevonedistat treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines derived from acute leukemias, lymphomas, multiple myeloma, and a range of solid tumor types. 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 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 [28-30].

Pevonedistat demonstrated pharmacodynamic and antitumor activity in solid tumor, lymphoma, and AML xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route. Very few preclinical models of HR MDS are available, and pevonedistat has not been tested specifically in HR MDS.

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 Practices (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 (≥600 mg/m^2). Mortality and/or moribundity were observed within 24 hours postdose as a result of gastrointestinal injury (mucoid/soft feces, diarrhea with some macroscopic correlations [reddened mucosa]) 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 Investigator's Brochure (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 HL60). The combination of pevonedistat and azacitidine in HL60 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 (HL60 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 HL60, 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 HL60 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, pevonedistat has been administered to 351 patients in clinical studies. These include 227 patients diagnosed with advanced malignancies including solid tumors, AML, melanoma, lymphoma, multiple myeloma, HR MDS, and acute lymphoblastic leukemia who participated in studies of single-agent pevonedistat. In ongoing combination studies: 42 elderly patients with treatment-naïve AML (Study C15009) have been treated with pevonedistat plus azacitidine; 58 patients with solid tumors have received combination treatments with docetaxel, gemcitabine, or a combination of carboplatin and paclitaxel (Study C15010); and 24 patients with advanced solid tumors have received a single IV dose of pevonedistat alone and in combination with the cytochrome P450 (CYP) 3A inhibitor probes, itraconazole or fluconazole, with the option to then continue receiving pevonedistat plus standard of care, either docetaxel, or carboplatin plus paclitaxel (Study C15011).

Pevonedistat has reported single-agent clinical activity in a phase 1 study (Study C15003) in relapsed/refractory AML patients [31]. In Study C15003, responses (complete responses and partial responses) were observed in a variety of patient settings, including postallogeneic transplant, therapy-related AML, and primary refractory AML. 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 Study C15003 had asymptomatic, transient increases in bone marrow blasts after achieving a response. In these 2 cases, bone marrow blasts increased from less than 5% to more than 20%, and then went down. In addition, another responder in that study had an asymptomatic, transient increase in bone marrow blasts before achieving a response. In that case, bone marrow blasts almost doubled before response. These 3 patients were allowed to remain on study because their investigators felt they were clinically benefiting from continued treatment despite changes in their bone marrow blast counts.

In addition, Study C15009 is currently evaluating the combination of escalating doses of pevonedistat on Days 1, 3, and 5 plus 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, age ≥60 years, who are unlikely to benefit from standard induction therapy [32]. Enrollment in Study C15009 is complete; however, final data are not yet available. Data available as of 26 September 2014 showed that 29 patients (median age 78.0 years; 17 [59%] men) had received pevonedistat 20 mg/m^2 (n=26) or 30 mg/m^2 (n=3). Primary diagnoses were 19 (66%) de novo AML and 10 (34%) secondary AML. Seventeen (59%) patients had intermediate-risk cytogenetics and 7 (24%) had adverse-risk cytogenetics (5 [17%] undetermined). The maximum tolerated dose (MTD) was determined to be 20 mg/m^2 pevonedistat in combination with 75 mg/m^2 azacitidine. During dose escalation, DLTs at the 30 mg/m^2 pevonedistat dose level included reversible Grade 2 increased bilirubin (n=1) and Grade 3/ Grade 4 increased transaminases (n=1) without clinical sequelae. In 1 of the 22 patients treated at the MTD, 1 additional DLT (Grade 4 aspartate aminotransferase [AST]/alanine aminotransferase [ALT] elevation) was seen in the expansion cohort; this patient was successfully re-challenged with a reduced pevonedistat dose. The most common adverse events (AEs; reported by ≥25% of patients) were constipation, febrile neutropenia, anaemia, decreased appetite, nausea, thrombocytopenia, and fatigue. Thirteen patients (45%) experienced drug-related AEs that were ≥Grade 3, including febrile neutropenia, anaemia, thrombocytopenia, and leukopenia. Additional preliminary safety information from Study C15009 is provided in Section 1.6.2. The nature and frequency of the reported toxicities (excluding DLTs) were similar to previous reports for azacitidine alone. Preliminary

pharmacokinetics (PK) data showed that the addition of azacitidine did not alter the known PK profile of single-agent pevonedistat.

In the 25 response-evaluable patients, there were 5 (20%) complete remissions (CRs), 2 (8%) complete remissions with incomplete blood count recovery (CRis), and 6 (24%) partial remissions (PRs), for an overall response rate of 52%. Eleven of the 13 responses occurred within the first 2 cycles of therapy and included 2 patients with bone marrow blasts >80%. Combination therapy with pevonedistat plus azacitidine was generally well tolerated. The characteristics of the observed responses suggest added benefit from the addition of pevonedistat compared with azacitidine alone in treatment-naïve AML patients, age ≥60 years, who are unlikely to benefit from standard induction therapy. Furthermore, the overall response rate is not appreciably different from that of the subset of low-blast AML patients (blast count <30%), further supporting the use of this combination in this study's patient population.

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.

1.4 Pharmacokinetics of Pevonedistat

1.4.1 Nonclinical Pharmacokinetics 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 is low in all animal species, likely as a result of the extensive partitioning of pevonedistat into red blood cells. 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 CYP3A4 with a small contribution from CYP2D6. Results from the completed drug-drug interaction (DDI) Study C15011 indicated that multiple-dose administration of fluconazole, a moderate CYP3A inhibitor, had no clinically relevant effects on the PK of pevonedistat.

Pevonedistat systemic exposure in the presence of itraconazole, a strong CYP3A inhibitor, was only minimally increased compared with that in the absence of itraconazole (geometric mean dose-normalized AUC_∞ ratio of 1.14 [90% CI, 1.07 to 1.23]). The 14% increase in the pevonedistat geometric mean dose-normalized AUC was not considered clinically meaningful when viewed in the context of pevonedistat overall PK variability (coefficient of variation in AUC_∞, 16%-34%), supporting inference of the lack of a clinically relevant effect of itraconazole, a strong CYP3A inhibitor on total systemic exposure (AUC) of pevonedistat (see Section 1.6.3). Pevonedistat does not inhibit CYP1A2, 2C9, 2C19, 2D6, and 3A4/5, and weakly and reversibly inhibits both CYP2B6 and 2C8; it does not induce CYP1A2, 2B6, and 3A4/5. When viewed in the context of clinically relevant concentrations at 20 mg/m^2 (mean single-dose maximum [peak] concentration [C_{max}] of ~0.5 µM), pevonedistat is unlikely to affect the PK of drugs that are metabolized by these CYP enzymes.

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 (concentrations producing 50% inhibition [IC_{50}] of 6.3 µM). Additional transport studies with organic anion-transporting polypeptides (OATP) in sandwich-cultured human hepatocytes showed that pevonedistat can inhibit the hepatic uptake of estrone-3-sulfate (IC_{50} of 29.1 µM) while inhibition of OATP-mediated uptake of simvastatin and lovastatin (IC_{50} of 0.4-4.9 µM and 0.9 µM, respectively) was observed in some, but not all, donors. On the basis of these data, pevonedistat at clinically relevant concentrations is unlikely to affect the PK of other drugs that are known BCRP or OATP substrates (IC_{50} >10-fold the unbound C_{max} even with the lowest estimated value), whereas the potential exists, albeit low, for drug interactions with BCRP inhibitors. Refer to Section 1.6.3 for a summary of potential clinical DDIs, and Sections 6.4 and 6.5 for excluded and permitted concomitant medications in this study.

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

1.4.2 Clinical Pharmacokinetics

Clinical pharmacokinetic data are summarized in Section 5.2 of 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. 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 a daily area under the plasma concentration-time curve ($AUC_{0\text{-}24hr}$) that increased proportionately with dose. Consistent with in vitro data, pevonedistat was also found to extensively partition in human blood (mean blood-to-plasma concentration ratio of ~65) with observed concentrations of pevonedistat in whole blood and plasma declining in parallel over 24 hours. Upon exploration of the effects of patient-specific covariates on pevonedistat population PK, body size and age influenced clearance of pevonedistat, while only body size was important for all volume of distribution parameters. Additionally, data are available in 29 treatment-naïve, elderly patients with AML 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) [32]. These data indicate that pevonedistat PK remains unaffected by 5 continuous days of azacitidine dosing when compared to single-agent pevonedistat data from the earlier study in patients with AML (Study C15003).

1.5 Study Rationale

MDS include a heterogeneous group of myeloid disorders characterized by ineffective hematopoiesis and transformation to AML. Treatment with azacitidine increases OS in patients with HR MDS relative to conventional care [13]. Consequently, azacitidine is approved in many countries as a single agent in HR MDS.

Pevonedistat is an investigational, first-in-class inhibitor of the NEDD8-activating enzyme that has reported single-agent clinical activity in a phase 1 study in patients with relapsed/refractory AML [31]. Based on nonclinical studies in AML models that demonstrated a synergistic lethality in cell lines and tumor regression in murine xenografts when pevonedistat was combined with azacitidine, pevonedistat is being studied in combination with azacitidine in treatment-naïve elderly patients with AML who are unlikely to benefit from standard induction therapy (Study C15009). Preliminary results suggest that 20 mg/m^2 pevonedistat plus azacitidine is generally well tolerated and demonstrates early signs of clinical activity [32].

1.5.1 Rationale for Study Population

Given the overlapping treatments and pathophysiology between HR MDS and AML, this phase 2 study will evaluate OS and EFS (in HR MDS or CMML, an event is defined as

transformation to AML or death; in low-blast AML, an event is defined as death) of the combination of pevonedistat and azacitidine compared with single-agent azacitidine as a treatment for HR MDS or CMML or low-blast AML. Patients with CMML are included because CMML shares clinical and biological features with MDS, has a similar variable clinical course, and treatment modalities for the 2 diseases are also similar (see Section 1.1.1). Patients with CMML were also included in randomized studies of azacitidine conducted in the United States (US) and the European Union with similar response rates to patients with MDS [13,27]. The rationale for including low marrow blast count (20%-30%) WHO-defined AML is because low marrow blast count AML had been previously classified as refractory anemia with excess blasts in transformation (RAEB-t), which was part of the MDS spectrum, and it is a population of patients with AML who have been shown to benefit from azacitidine-based therapy (see Section 1.1.1).

1.5.2 Rationale for the Combination of Pevonedistat Plus Azacitidine

The rationale for combining pevonedistat with azacitidine in patients with AML and MDS is 2-fold; namely, the single-agent activity observed with azacitidine [13] and pevonedistat [33] 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.

1.5.3 Rationale for Dose and Schedule of Study Drugs

The choice of doses and schedules for this study was based on Study C15009, which established the MTD of pevonedistat as 20 mg/m^2 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 liver function tests (LFTs; see Section 1.3 and the IB for more information).

The commonly used schedule of azacitidine administration in the United States is a 5-on/2-off (weekend)/2-on schedule to avoid the logistical limitations associated with administering drugs to patients during the weekend. According to oncologist/hematologist surveys conducted by the sponsor, of the patients treated with azacitidine for AML in the United States, approximately 70% follow this schedule. Garcia et al conducted a retrospective evaluation of 3 schedules of azacitidine administration in 181 patients with MDS. Evaluated patients received 75 mg/m^2 azacitidine on one of the following schedules: 5 days, 5-on/2-off/2-on, or daily for 7 days. The overall response rates (38%, 71%, and 52%,

respectively) favored 5-on/2-off/2-on administration of azacitidine over a 7-day administration, with p = 0.0418. All schedules were well tolerated [34].

In this study, azacitidine may be administered using either the SC or the IV route of administration, given that comparable systemic exposures ($AUC_{0\text{-}48hr}$) to azacitidine were achieved following either route in Study C15009. Furthermore, it has been reported that azacitidine is generally well tolerated regardless of the route of administration [35], which is also supported by preliminary data from Study C15009.

As detailed in Section 1.3, some patients in Study C15003 (single-agent pevonedistat in patients with relapsed/refractory AML) derived clinical benefit from continuing study treatment despite changes in their bone marrow blast counts. Standard MDS guidelines [36] also recommend treatment for 6 cycles without altering dose or frequency of azacitidine regardless of cytopenias. Patients with HR MDS or CMML may be allowed to continue study treatment (either treatment arm) if they meet the criteria for progressive disease based only on bone marrow blast count (without AML transformation) if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients with low-blast AML, in this study, may also be allowed to continue study treatment (either treatment arm), even if they meet the criteria for progressive disease based only on bone marrow blast counts, if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment. If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study.

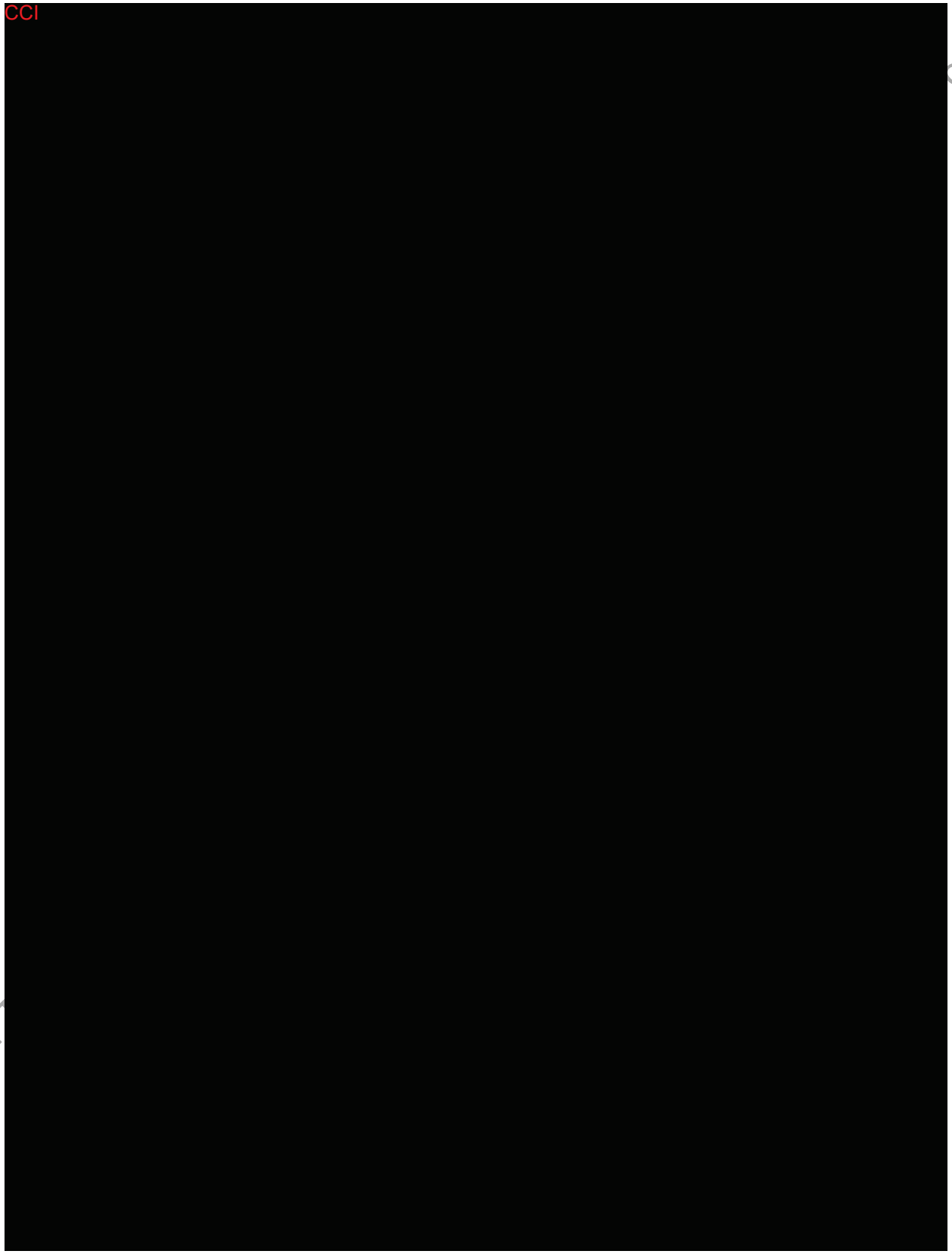
1.5.4 Rationale for Molecular Analyses

CCI [redacted]

Both AML and MDS are heterogeneous diseases with respect to both tumor biology and clinical outcome. Various studies confirm that survival for individual patients in both diseases is heavily influenced by the specific molecular pathology of their tumors. Along with age and performance status, cytogenetics are a key clinical predictor, and cytogenetic findings are incorporated into risk categorization schemes to guide treatment.

The European LeukemiaNet integrates cytogenetics and molecular features of 3 key AML genes (FLT3 ITD, CEBP, and NPM1) to classify patients into 4 prognostic risk groups [37].

CCI



CCI

[redacted]

Leukemic cells that remain in the bone marrow following treatment are a major cause of disease relapse. Measurable residual disease (MRD) testing provides the sensitivity and specificity to identify the presence of these residual cells. Studies have shown that the sensitive detection of a leukemia-specific marker (eg, a mutation in the gene encoding nucleophosmin [*NPM1*]) could improve prognostication by identifying submicroscopic disease during remission [51]. Assessment of MRD is receiving recognition as a potential tool to assess the quality of response after chemotherapy and to plan post-remission strategies. PCR and multiparametric flow cytometry have become the most popular methods to investigate MRD in AML [52]. Methods to assess MRD by next-generation sequencing (NGS) are also being explored [53].

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

1.5.5 Rationale for Health-Related Quality of Life Assessments

When caring for patients with advanced and life-threatening diseases such as cancer, preserving their health-related quality of life (HRQOL) and reducing symptom burden are among the most important therapeutic goals. However, there are limited data on patient reported outcomes (PROs) among patients with HR MDS. In previous randomized clinical trials among patients with MDS, patients on the azacitidine arm experienced improvement in HRQOL as assessed by the EORTC-QLQ-C30 PRO instrument [62].

To compare the impact of treatment between the 2 patient groups in this study, HRQOL will be assessed by 3 instruments: EORTC-QLQ-C30 and EQ-5D-5L (all patients) and the QOL-E (US patients only). Data from these 3 instruments will facilitate assessment of important general, cancer-specific, and MDS-specific HRQOL domains and items, and ascertainment of how these may be correlated with certain clinical outcomes.

The EORTC-QLQ-C30 [63], designed to assess health-related quality of life in a wide range of cancer patient populations, has been administered in multiple randomized clinical trials of patients with MDS [62,64].

While the EORTC-QLQ-C30 assesses important HRQOL domains including global health status/quality of life, functioning, and symptoms over the past week, the QOL-E was developed specifically for patients with MDS, with evidence for reliability and validity in this patient population [65]. As such, it is used to assess the specific impact of MDS on HRQOL that is not measured in general non–MDS-specific instruments.

Because oncology therapies may positively or negatively affect a patient's quality of life, a common methodological approach used to quantify this effect is to "quality-adjust" survival rates in comparative treatment arms. The resulting data, referred to as quality-adjusted life years (QALYs), provide a measure of both the length and quality of life and are used for economic evaluation of new therapies. The data required for the assessment for QALY is captured by EQ-5D-5L.

Refer to Section 7.4.16 for additional details on the components and administration of these questionnaires.

1.6 Potential Risks and Benefits

1.6.1 Azacitidine

In clinical studies, adverse reactions to azacitidine were qualitatively similar between the IV and SC routes of administration [35]. In clinical studies with SC administration of azacitidine, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of azacitidine. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of SC treatment compared with later cycles included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia. There did not appear to be any adverse reactions that increased in frequency over the course of treatment.

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

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

Refer to the VIDAZA (azacitidine) US Prescribing Information (USPI) [35],or the European Union (EU) Summary of Product Characteristics (SmPC) [66], as applicable, for the most recent information regarding the anticipated risks and benefits of azacitidine.

1.6.1.1 Anemia, Neutropenia, and Thrombocytopenia

Azacitidine causes anemia, neutropenia, and thrombocytopenia. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response (see Section 6.3.2.1).

1.6.1.2 Severe Pre-existing Hepatic Impairment

Caution is needed in patients with liver disease when administering azacitidine. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients

with baseline albumin <30 g/L [67]. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

1.6.1.3 Renal Abnormalities

Patients with renal impairment should be closely monitored for toxicity because azacitidine and its metabolites are primarily excreted by the kidneys. Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with IV azacitidine in combination with other chemotherapeutic agents for non-MDS conditions. Renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L), developed in 5 patients with chronic myelogenous leukemia treated with azacitidine and etoposide.

1.6.2 Pevonedistat Plus Azacitidine

In the ongoing clinical study of the combination of pevonedistat and azacitidine in treatment-naïve patients with AML, age ≥60 years (Study C15009), among 25 response-evaluable patients, 28% had a best response of CR or CRi (26 September 2014 data cut) [32]. A majority of the responses have occurred within the first 2 cycles. Responses have been seen in patients with hyperproliferative phenotypes and adverse cytogenetics. 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.

Preliminary safety data (as of 28 August 2015) from 56 patients in Study C15009 who received ≥1 dose of the combination of pevonedistat and azacitidine indicate that the very common AEs (≥10% of patients) have included constipation (43%), anemia (30%), fatigue (30%), febrile neutropenia (29%), decreased appetite (29%), thrombocytopenia (27%), dyspnea (25%), nausea (25%), neutropenia (20%), cough (16%), vomiting (16%), pyrexia (14%), pneumonia (14%), chills (13%), leukopenia (13%), pain in extremity (13%), insomnia (13%), sleep disturbances (13%), diarrhea (11%), edema peripheral (11%), hypoalbuminemia (11%), hypokalemia (11%), upper respiratory tract infections (11%), urinary tract infections (11%), oropharyngeal pain (11%), and anxiety (11%).

Drug-related ≥ Grade 3 adverse events include thrombocytopenia 8 (14%), febrile neutropenia 7 (13%), anemia 7 (13%), leukopenia 4 (7%), neutropenia 3 (5%), AST increased 4 (7%), ALT increased 3 (5%), transaminases increased 2 (4%), neutrophil count

decreased 1 (2%), blood pressure increased 1 (2%), pharyngitis 1 (2%), upper respiratory tract infections 1 (2%), constipation 1 (2%), cardiac failure 1 (2%), and heart failure 1 (2%).

The most detailed information on risks is provided in the Investigator's Brochure and the Developmental Core Safety Information (DCSI) located within the Investigator's Brochure.

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

Hepatotoxicity: Hepatotoxicity has been noted following administration of pevonedistat in patients with advanced malignancy, including elevations of liver transaminases (up to Grade 4), alkaline phosphatase (up to Grade 3), and bilirubin (up to Grade 3). Grade 1 through 4 increases in alanine aminotransferase and aspartate aminotransferase have been observed in patients receiving single-agent pevonedistat for relapsed and/or refractory AML. The patients experiencing these changes in laboratory values have been asymptomatic. This type of elevation in transaminases had been observed previously in patients treated with pevonedistat. The elevations in laboratory values have been reversible with dose modification including dose delay and reduction. Patients with elevated transaminases have been successfully rechallenged at lower doses.

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

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

Potential risks that are derived from findings in animal studies in rats and dogs include myocardial degeneration and thrombosis, cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure, increased diastolic blood

pressure, pulmonary hypertension, enteropathy (including dehydration and electrolyte loss) with secondary sepsis, effects on testes and ovaries that represent a reproductive hazard including sterility, increased developmental risk to fetus or embryo, decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, high) (this finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the doses), prolongation of the activated thromboplastin time (aPTT), and local tissue injury when administered subcutaneously (SC). Additional details may be found in the current IB.

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

In Study C15009, patients receive azacitidine as either an IV infusion or subcutaneous injection. Preliminary data indicate that the route of azacitidine administration has no apparent effect on the safety profile of pevonedistat plus azacitidine.

1.6.3 Potential for Drug-Drug Interactions

No formal clinical assessments of DDIs between azacitidine and other agents have been conducted. Please consult the VIDAZA USPI (Clinical Pharmacology [Section 12.3], Drug-Drug Interactions) for additional information [35].

The potential risk of DDIs between pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data (see IB and Section 1.4). Study C15011, a phase 1 study to assess 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 (see Section 1.4.1) was completed. Based on results from C15011, administration of pevonedistat with moderate and strong CYP3A inhibitors is permitted in this study, while use of strong CYP3A inducers should be avoided. As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored as the DDI potential between pevonedistat and other drugs has not been formally studied in humans. Patients should also be instructed to consult with the investigator before taking any new medications, including over-the-counter products and herbal supplements.

See Section 6.4 for information on concomitant medications that are prohibited and Section 6.5 for information on medications that are permitted during this study.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is:

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

2.2 Secondary Objectives

The secondary objectives are:

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine improves event-free survival (EFS) when compared with single-agent azacitidine; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death (see Section 7.4.21).

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine improves 6-month and 1-year survival rates when compared with single-agent azacitidine.

- To determine in patients with HR MDS or CMML whether the combination of pevonedistat and azacitidine delays time to AML transformation when compared with single-agent azacitidine.

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves the rate of complete remission (CR) (composite CR [CR+ CRi] in patients with low-blast AML), CR plus partial remission (composite CR + PR for patients with low-blast AML), overall response, and/or CR (not including CRi) in low-blast AML. Overall response in HR MDS or CMML is defined as CR + PR +

hematologic improvement (HI); overall response in low-blast AML is defined as CR + CRi + PR.

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves the rate of CR (composite CR [CR + CRi] in patients with low-blast AML), CR + PR (composite CR + PR in patients with low-blast AML), the overall response rate (ORR), as well as CR (not including CRi) in low-blast AML by Cycle 4.

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves duration of CR (composite CR [CR + CRi] in patients with low-blast AML), CR + PR (composite CR + PR in patients with low-blast AML), overall response, and/or CR (not including CRi) in patients with low-blast AML.

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine improves time to first CR (CR for HR MDS/CMML and low-blast AML; CR + CRi [composite CR] for low-blast AML), or PR when compared with single-agent azacitidine.

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine delays time to subsequent therapy when compared with single-agent azacitidine. Subsequent therapy is defined as agent(s) with antileukemic/anti-MDS activity (eg, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine improves rate of transfusion independence when compared with single-agent azacitidine. RBC or platelet transfusion independence requires that the patient receive no RBC or platelet transfusions, respectively, for a period of at least 8 weeks.

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine reduces the percent of patients who have

at least one inpatient hospital admission(s) related to HR MDS or CMML, or low-blast AML when compared with single-agent azacitidine.

- To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine delays time to PD, relapse, or death when compared to single-agent azacitidine.
- To evaluate in patients with HR MDS or CMML and low-blast AML the safety of the combination of pevonedistat and azacitidine when compared with single-agent azacitidine.
- To collect in patients with HR MDS or CMML and low-blast AML plasma concentration-time data for pevonedistat to contribute to future population PK analyses of pevonedistat.

2.3 Exploratory Objectives

The exploratory objectives include:

CCI

[redacted]

CCI

[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is:

- OS

3.2 Secondary Endpoints

The secondary endpoints are:

- EFS; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death (see Section 7.4.21).
- Six-month and 1-year survival rates.
- Time to AML transformation in patients with HR MDS or CMML.
- CR (CR for HR MDS and CMML; CR + CRi [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) + PR, overall

response (CR + PR + HI for HR MDS and CMML; CR + CRi + PR for low-blast AML), CR (not including CRi) in low-blast AML.

- CR (CR for HR MDS and CMML; CR + CRi [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) + PR, overall response (CR + PR + HI for HR MDS and CMML; CR + CRi + PR for low-blast AML) by Cycle 4, CR (not including CRi) in low-blast AML by Cycle 4.

- Duration of CR (CR for HR MDS and CMML, CR + CRi [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) + PR, overall response (CR + PR + HI for HR MDS and CMML; CR + CRi + PR for low-blast AML), and duration of CR (not including CRi) in low-blast AML.

- Time to first CR (CR for HR MDS/CMML and low-blast AML; CR + CRi [composite CR] for low-blast AML) or PR for HR MDS/CMML and low-blast AML.

- Time to subsequent therapy.

- RBCs and platelet-transfusion independence.

- Percentage of patients with at least 1 inpatient hospital admission related to HR MDS or CMML (collected through transformation to AML or until initiation of subsequent therapy, whichever occurs first) or low-blast AML (collected through AML progression or until initiation of subsequent therapy, whichever occurs first).

- Time to PD, relapse, or death.

- AEs and serious adverse events (SAEs), abnormal clinical laboratory values, Eastern Cooperative Oncology Group (ECOG) performance status, ECGs, and vital sign measurements.

3.3 Exploratory Endpoints

The exploratory endpoints include:

CCI

CCI

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This study is a multicenter, global, randomized, controlled, open-label, phase 2 clinical study of the combination of pevonedistat and azacitidine versus single-agent azacitidine administered in patients with HR MDS or CMML and low-blast AML (see inclusion criteria 2 and 3 for definitions) who have not previously received a hypomethylating agent. Patients with nonproliferative CMML (ie, white blood cell [WBC] <20,000/µL) are included because these patients were also included in both randomized studies of azacitidine conducted in the US and the European Union with similar response rates to patients with MDS.

General eligibility may be assessed prior to the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events, formal screening will occur during the Screening period, which may last up to 28 days prior to randomization. The

sponsor's project clinician (or designee) will confirm patient eligibility prior to randomization by the investigator.

It is expected that approximately 117 patients will be enrolled in this study. Once enrolled, patients (MDS, CMML, and low-blast AML) will be randomized at a 1:1 ratio to receive study drug (either single-agent azacitidine or the combination of pevonedistat and azacitidine) in 28-day treatment cycles. All patients will be stratified into 4 categories: low-blast AML, IPSS-R risk groups of very high, high, or intermediate for MDS/CMML [2]. Note that patients with HR MDS/CMML with indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points, ie, intermediate, for determining overall Prognostic Risk Category/Score; see Section 7.4.4. All patients will receive azacitidine (75 mg/m^2 [IV or SC]) on Days 1 through 5, Day 8, and Day 9. Patients randomized to the combination arm will also receive pevonedistat (20 mg/m^2 via 60 ([±10]-minute infusion) on Days 1, 3, and 5. Modifications to the dose and schedule may be allowed as detailed in the Schedule of Events and Section 6.1.

Patients, including those who achieve a CR, may receive study treatment until they experience unacceptable toxicity, relapse, transformation to AML, or PD as defined in Section 7.4.21. **Patients with HR MDS or CMML may be allowed to continue study treatment (either treatment arm) if they meet the criteria for progressive disease based only on bone marrow blast count (without AML transformation) if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients with low-blast AML in this study may also be allowed to continue study treatment (either treatment arm), even if they meet the criteria for progressive disease based only on bone marrow blast counts, if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment.** Patients may choose to discontinue therapy at any time.

Patients will attend the End-of-Treatment (EOT) visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner. After the EOT visit, patients will enter EFS follow-up (for patients with HR MDS or CMML) or response follow-up (for patients with low-blast AML), with study visits every 3 months, to include physical exam, clinical blood tests, HRQOL assessments,

hospitalization assessment, bone marrow aspirate sampling, and disease assessment, if their disease has not transformed to AML (for patients with HR MDS or CMML) or progressed (for patients with low-blast AML), and they have not started subsequent therapy. Patients will enter OS follow-up (contacted every 3 months to document subsequent therapies and survival status) when they have confirmed transformation to AML (for patients with HR MDS or CMML) or experienced progressive disease (for patients with low-blast AML) or have started subsequent therapy.

Disease response assessments for all patients with HR MDS or CMML will be based on the Modified International Working Group (IWG) response criteria for MDS [3] as detailed in Section 7.4.21. Disease response assessments for patients with low-blast AML will be based on the Revised Recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia as detailed in Section 7.4.21 [4]. Formal disease assessments for study endpoints will be determined based on local bone marrow aspirate blast counts and transfusions, and central lab data (local lab data may be used for time-sensitive clinical decisions).

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

A bone marrow aspirate and biopsy will be collected at Screening, and bone marrow aspirates will be collected during treatment and follow-up for blast count evaluation (to inform disease burden assessment). CCI [redacted]

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

Adverse events and ECOG performance status will be assessed, and ECGs, clinical laboratory values, and vital signs will be obtained, to evaluate the safety and tolerability of the study drug treatments. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [68]. Dose modification guidelines are presented in Section 6.3.

CCI

[redacted]

4.2 Number of Patients

Approximately 117 patients (randomized in a 1:1 ratio) will be enrolled in this study from approximately 80 study centers globally. Enrollment is defined as when the patient is randomized onto study treatment.

4.3 Duration of Study

Patients, including those who achieve a CR, may receive study treatment until they experience PD or discontinuation for any other reason outlined in Section 7.5. Patients will be followed until approximately 60% of patients with HR MDS/CMML have experienced OS events, or termination of the study by the sponsor. Patients who are still receiving study treatment and continuing to derive clinical benefit may continue to receive pevonedistat at the discretion of the sponsor; the continuation of treatment may occur in a manner other than under the study protocol, in accordance with local regulations.

After discontinuing study treatment (including the EOT visit), patients will be followed for survival, subsequent therapy, and transformation to AML (for patients with HR MDS or CMML), or progression and relapse from CR (patients with low-blast AML).

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.

2. Morphologically confirmed diagnosis of MDS, nonproliferative CMML (ie, with WBC <20,000/µL), or low-blast AML based on 1 of the following:

   French-American-British (FAB) Classifications [5]:

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

   OR

   World Health Organization (WHO) Classifications [6,7]:

   - Refractory anemia with excess blasts-1 (RAEB-1 – defined as having 5% to 9% myeloblasts in the bone marrow).
   - Refractory anemia with excess blasts-2 (RAEB-2 – defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood).
   - Chronic Myelomonocytic Leukemia-2 (CMML-2 – defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood).
   - Chronic Myelomonocytic Leukemia-1 (Although CMML-1 is defined as having <10% myeloblasts in the bone marrow and/or <5% blasts in the blood, these patients may enroll only if bone marrow blasts ≥5%).
   - WHO-defined AML with 20% to 30% myeloblasts in the bone marrow (defined in this protocol as "Low-Blast AML") and ≤30% myeloblasts in peripheral blood who are considered by investigator to be appropriate for azacitidine-based therapy.

3. For patients with MDS and CMML, prognostic Risk Category, based on the Revised International Prognostic Scoring System (IPSS-R) [2], of:

   - Very high (>6 points),
   - High (>4.5 - 6 points), or
   - Intermediate (>3 – 4.5 points): a patient determined to be in the Intermediate Prognostic Risk Category is only allowable in the setting of ≥5% bone marrow myeloblasts.

   Patients with indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points (ie, intermediate) for determining overall Prognostic Risk Category/Score (see Section 7.4.4).

4. ECOG performance status of 0 to 2 (see Section 15.1).

5. Clinical laboratory values within the following parameters (repeat within 3 days before the first dose of study drug if laboratory values used for randomization were obtained more than 3 days before the first dose of study drug):

   - Albumin >2.7 g/dL.
   - *Total* bilirubin <upper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if *direct* bilirubin ≤ 1.5 x ULN of the *direct* bilirubin.
   - ALT and AST ≤2.5 × ULN.
   - Creatinine clearance ≥50 mL/min (see Section 15.2).
   - Hemoglobin >8 g/dL. Patients may be transfused to achieve this value. Elevated indirect bilirubin due to post-transfusion hemolysis is allowed.

6. ***For patients with CMML:*** WBC count <20,000/µL before administration of the first dose of study drug on Cycle 1 Day 1; patients must have been off hydroxyurea for at least 1 week prior to WBC count assessment.

7. Ability to undergo the study-required bone marrow sample collection procedures.

8. Suitable venous access for the study-required blood sampling (ie, including PK [redacted]).

9. Female patients who:

   - Are postmenopausal (see Section 15.3) 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 15.4), at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

   Male patients, even if surgically sterilized (ie, status postvasectomy), who:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods 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.)

10. 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. Previous treatment with decitabine or azacitidine or other hypomethylating agent.
2. Acute promyelocytic leukemia as diagnosed by morphologic examination of bone marrow, by fluorescent in situ hybridization or cytogenetics of peripheral blood or bone marrow, or by other accepted analysis.
3. Eligible for allogenic stem cell transplantation.
4. Patients with MDS, CMML, or low-blast AML, whose only site of disease is extramedullary, eg, the skin.
5. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures or could limit patient expected survival to less than 6 months.
6. Treatment with any anti-leukemic/anti-MDS therapies (eg, lenalidomide, cytarabine, anthracyclines, purine analogs) or with any investigational products within 14 days before the first dose of any study drug.
7. Known hypersensitivity to mannitol.
8. Active uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, or septicemia.
9. Major surgery within 14 days before first dose or a scheduled surgery during study period; insertion of a venous access device (eg, catheter, port) is not considered major surgery.
10. Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone resection.
11. Life-threatening illness unrelated to cancer.

12. Prothrombin time (PT) or aPTT > 1.5 ULN or active uncontrolled coagulopathy or bleeding disorder.

13. Known human immunodeficiency virus (HIV) seropositive.

14. Known hepatitis B surface antigen seropositive, or known or suspected active hepatitis C infection. Note: Patients who have isolated positive hepatitis B core antibody (ie, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load.

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

16. Known cardiopulmonary disease defined as unstable angina, clinically significant arrhythmia, congestive heart failure (New York Heart Association [NYHA] Class III or IV; see Section 15.5), and/or myocardial infarction within 6 months prior to first dose, or severe pulmonary hypertension. As an example, well-controlled atrial fibrillation would not be an exclusion whereas uncontrolled atrial fibrillation would be an exclusion.

17. Treatment with strong CYP3A inhibitors or inducers (see Section 15.6) within 14 days before the first dose of pevonedistat.

18. Systemic antineoplastic therapy or radiotherapy for other malignant conditions within 12 months before the first dose of any study drug, except for hydroxyurea.

19. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

20. Female patients who intend to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

21. Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

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).

The first dose of study drug must be administered within 5 days of randomization on study. It is strongly recommended that dosing for both treatment arms occur on the days specified (ie, azacitidine dosing on Days 1-5, 8, and 9; pevonedistat dosing on Days 1, 3, and 5). However, dosing of either drug may be delayed for safety reasons or other unavoidable circumstances (eg, weather affecting clinic accessibility). If pevonedistat dosing is delayed, a minimum of 1 full calendar day 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. For the combination arm, pevonedistat and azacitidine should always be administered on the same day (eg, instead of pevonedistat dosing on Days 1, 3, and 5, it would be acceptable to dose on Days 1, 5, and 8). If dosing is adjusted, study procedures should be performed on the actual day of dosing.

The amount of study drug (pevonedistat and/or azacitidine, as applicable) to be administered will be based on body surface area (BSA). BSA will be calculated using a standard formula (see example in Section 15.8) 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.

6.1.1 All Patients – Azacitidine Dosing

All patients will receive azacitidine (75 mg/m^2 [IV or SC, per investigator's choice]) on Days 1 through 5, Day 8, and Day 9 of each treatment cycle. The investigator, without approval of the sponsor's project clinician, may choose to switch the route of azacitidine administration at any time based on standard of care, clinical preference, or convenience. Please see the most recent VIDAZA (azacitidine) USPI [35] or EU SmPC [66], for details on azacitidine administration.

6.1.2 Additional Instructions for the Combination Arm – Pevonedistat Plus Azacitidine Dosing

Patients assigned to the Combination Pevonedistat Plus Azacitidine Arm will receive azacitidine as described in Section 6.1.1 and will also receive pevonedistat (20 mg/m^2) via

60 (±10) minute infusion on Days 1, 3, and 5. All doses must be taken as outlined in the Schedule of Events.

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 infusion may be slowed or stopped and restarted for any associated infusion-related reactions. All infusion times must be recorded. The total time from drug reconstitution to end of infusion must not exceed 6 hours.

The entire content of the pevonedistat IV bag will be infused at a constant rate over 60 (±10) minutes. The start and end time of IV infusion should be recorded accurately, particularly in Cycle 1, when PK assessments are performed. 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.

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, and between 30 and 60 minutes after completion of administration of IV azacitidine.

6.2 Reference/Control Therapy: Azacitidine

Azacitidine is a chemical analogue of cytidine that is widely used for the treatment of patients with AML. A phase 3, randomized, open-label, international study compared azacitidine (75 mg/m^2 SC daily for 7 days, every 28 days) with investigator selected, conventional care regimens (CCRs) (eg, best supportive care, low dose cytarabine, or intensive chemotherapy) in 358 patients with HR MDS as defined at that time [13].

Approximately one third (n=113) of the patients in this study had refractory anemia with excess blasts in transformation (RAEB-t; 20%-30% bone marrow blasts); under the 2008 WHO revised criteria, RAEB-t is now defined as AML [6]. A subanalysis of the study compared the relative efficacy and safety of azacitidine versus CCR in this patient subgroup (median age, 70 years) [69]. Of these 113 patients with WHO-defined AML, 86% were considered unfit for intensive chemotherapy. Two-year OS rates were higher with azacitidine versus CCR in the patients considered unfit for intensive chemotherapy (51% vs 13%, respectively, p=0.0003). In addition, azacitidine was associated with fewer total days

in the hospital (26.0 vs 50.9 days per patient-year; relative risk=0.48; 95% confidence interval [CI] 0.44-0.52; p<0.0001) than CCR. In patients with unfavorable cytogenetics, median OS in the azacitidine (n=14) and CCR (n=13) groups was 12.3 and 5.3 months, respectively (hazard ratio=0.66; 95% CI 0.26-1.68; p=0.38), whereas the 2-year OS rate was 38% for azacitidine, with no patients surviving more than 20 months in the CCR group (p=0.01) [69].

In a randomized phase 3 trial of azacitidine versus CCR in older patients with newly diagnosed AML, the median OS with azacitidine was 10.4 months, a 3.8 month (58%) increase over CCR. One-year survival with azacitidine was 47%, a 36% increase over CCR. Although the study did not reach statistical significance for its primary endpoint of OS (p=0.08), azacitidine demonstrated a clinically meaningful improvement. A sensitivity analysis of OS censoring at subsequent AML therapy demonstrated a statistically significant benefit for azacitidine versus CCR (12.1 vs 6.9 months, respectively; p=0.0147) [70].

6.3 Dose Modification Guidelines

6.3.1 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 to ≤Grade 1. For pevonedistat, a minimum of 1 full calendar day 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. If azacitidine is held for whatever reason, it may be resumed to complete a full treatment course as long as the full 7 doses are completed within the first 14 days of the cycle.

If dosing is interrupted within a cycle because of drug-related toxicity, and if the investigator and the sponsor's project clinician (or designee) agree that 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 toxicity not related to drug (eg, disease-related toxicity), although a similar dose reduction is permitted, in general it is discouraged. If the reduced dose is well tolerated and the toxicity leading to dose reduction was ≤Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor's project clinician (or designee). For specific guidelines on azacitidine and pevonedistat dose reductions, see Sections 6.3.2 and 6.3.3).

Initiation of a New Cycle

Treatment with study drugs will be repeated every 28 days. It is strongly recommended that dosing for both treatment arms occur on the days specified. However, the initiation of a new cycle may be delayed for safety reasons or other unavoidable circumstances (eg, weather affecting clinic accessibility). For therapy to resume, nonhematologic 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 sponsor's project clinician (or designee). Criteria for dosing in a new cycle related to hematologic toxicities are detailed for azacitidine in Section 6.3.2.1 and for pevonedistat in Section 6.3.2.2.

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 re-evaluated to determine whether the criteria for retreatment have been met. A dose reduction (as detailed in Sections 6.3.2 and 6.3.3) would be triggered if treatment is delayed for >2 weeks because of incomplete recovery from treatment-related toxicity. If the reduced dose is well tolerated and the toxicity leading to dose reduction was ≤Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor's project clinician (or designee).

6.3.2 Dose Modification for Hematologic Toxicities

6.3.2.1 Azacitidine

Dose reduction or delays of azacitidine for hematologic toxicities (including fever and neutropenia) during the first 6 cycles of therapy are strongly discouraged, as it may impact patient outcome. Any potential dose reduction should be discussed and agreed first with the sponsor's project clinician (or designee).

For hematologic AEs, the start of a new treatment cycle should be delayed and/or dose modifications should be considered if:

- Absolute neutrophil count (ANC) is <500/µL. For patients with disease-related neutropenia, physician discretion may be used to initiate therapy with ANC ≥50% of baseline (baseline from the start of the previous cycle). In general, the use of growth factors should be restricted. However, to avoid dose delay, patients who experience Grade 4 neutropenia (ANC <500/µL) with or without fever may receive granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating

factor (GM-CSF) between days 28 to 42 days of azacitidine monotherapy or combination after discussion and agreement with the sponsor's project clinician (or designee). Any use of growth factors will be documented in the electronic case report form (eCRF). Patients who receive myeloid growth factors will not be included in assessment of neutrophil response.

- Platelet count is <20,000/μL. For patients with disease-related thrombocytopenia, physician discretion may be used to initiate therapy with platelet count ≥50% of baseline (baseline from the start of the previous cycle). If the above criteria are not met, the start of the new cycle will be delayed until the above criteria are met. If a low ANC or platelet count causes the delay of the start of the new cycle of more than 2 weeks, then the azacitidine dose will be decreased to 50 mg/m^2 when treatment is resumed. Treatment may be held up to 6 weeks (42 days) due to toxicity before patient must be removed from protocol therapy.

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

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

6.3.2.2 Pevonedistat

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

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

6.3.3 Dose Modification for Nonhematologic Toxicities

6.3.3.1 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 prescribing information [35] and/or institutional guidelines. Similarly, if unexplained elevations in serum creatinine or blood urea nitrogen (BUN) occur, the next cycle should be delayed until values return to normal or baseline values, and the dose should be reduced by 50% on the next treatment course.

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

6.3.3.2 Pevonedistat

Pevonedistat Dose Adjustment Based on Serum Transaminases and Total Bilirubin

It is anticipated that LFTs (AST, ALT, and occasionally bilirubin) may be elevated for approximately 48 hours following the end of pevonedistat infusion on Cycle 1 Day 1.

For elevated LFTs of Grade 2 or 3 that occur on or after Cycle 1 Day 3, pevonedistat should be held; once the elevated AST or ALT returns to ≤Grade 1, and/or elevated bilirubin returns to ≤1.5×ULN or the patient's baseline level, pevonedistat dose may be resumed at 20 mg/m^2. For pevonedistat, a minimum of 1 full calendar day between any 2 doses should be maintained, and a maximum of 3 doses of pevonedistat within the cycle must not be exceeded.

For elevated LFTs of Grade 4 that occur on or after Cycle 1 Day 3, the pevonedistat dose should be held for the remainder of the cycle; if the elevated AST or ALT returns to ≤Grade 1, and/or elevated bilirubin returns to ≤1.5×ULN or the patient's baseline level, then pevonedistat may be restarted at the next cycle at a reduced dose of 10 mg/m^2. If the toxicity returns to ≤Grade 1 or the patient's baseline status, pevonedistat may be re-escalated to 15 mg/m^2 for the next cycle. After 1 cycle at 15 mg/m^2, further re-escalation to 20 mg/m^2 may occur only after the patient's liver function test (AST, ALT, and bilirubin) have been confirmed to be ≤Grade 1, the same level as the patient's baseline values, or a level considered acceptable by the investigator and the sponsor's project clinician (or designee).

Pevonedistat Dose Adjustment Based on Hypophosphatemia

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

Pevonedistat Dose Adjustment for Other Toxicities

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

6.4 Excluded Concomitant Medications and Procedures

Prohibited concomitant therapies include investigational agents, androgens, supraphysiologic doses of corticosteroids, erythropoietin, thrombopoietin agonists (eg, eltrombopag and romiplostim) or chemotherapeutic agents active against MDS, CMML, or low-blast AML.

Medications that are generally excluded but are allowed with certain exceptions listed in Table 6.a (for the Single-Agent Azacitidine Arm) and Table 6.b (for the Combination Pevonedistat Plus Azacitidine Arm).

Table 6.a Concomitant Medications Excluded While Receiving Study Treatment: Single-Agent Azacitidine Arm

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 during the study treatment phase may be adjusted to control the level of circulating blast counts to no lower than 10,000/µL while on study treatment. The dosing of hydroxyurea and changes to dosing of hydroxyurea must be recorded.
Any investigational agent for MDS, CMML, or low-blast AML, or commercially available agents used in MDS, CMML, or low-blast AML, including androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]	

AML= acute myelogenous leukemia, CMML=chronic myelomonocytic leukemia, MDS=myelodysplastic syndromes.

Table 6.b Concomitant Medications Excluded While Receiving Study Treatment: Combination Pevonedistat Plus Azacitidine Arm

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 during the study treatment phase may be adjusted to control the level of circulating blast counts to no lower than 10,000/µL while on study treatment. The dosing of hydroxyurea and changes to dosing of hydroxyurea must be recorded.
Strong CYP3A inducers (see Section 15.6)	
Known BCRP inhibitors (ie, cyclosporine)	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), 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.
Any investigational agent other than pevonedistat, for MDS, CMML, or low-blast AML, or commercially available agents used in MDS, CMML, or low-blast AML, including androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]	

AML=acute myelogenous leukemia, BCRP=breast cancer resistance protein, CMML=chronic myelomonocytic leukemia, CYP=cytochrome P450, G-CSF=granulocyte colony-stimulating factor, GM-CSF=granulocyte macrophage colony-stimulating factor, MDS=myelodysplastic syndromes.

6.5 Permitted Concomitant Medications and Procedures

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

Table 6.c Concomitant Medications and Procedures Permitted During the Study

Therapy	Comment
Anti-platelet agents (eg, aspirin, clopidogrel) and anticoagulants	May be used in patients who have controlled coagulopathy at baseline, as well as those who develop a coagulopathy on study. Note that patients with active uncontrolled coagulopathy are excluded from enrollment as per Section 5.2.
Antiemetics for azacitidine	May be administered according to institutional guidelines.
Myeloid growth factors (eg,	In general, the use of myeloid growth factors is discouraged and should be

Table 6.c Concomitant Medications and Procedures Permitted During the Study

Therapy	Comment
G-CSF, GM-CSF)	restricted. For patients in CR, CRi, or marrow CR, growth factors may be used in specific circumstances after discussion with the project clinician or designee. Use of growth factors may also be used in patients with Grade 3 or Grade 4 febrile neutropenia after discussion and agreement with the project clinician or designee. Additionally, to avoid dose delays, patients who experience Grade 4 neutropenia (ANC <500/µL) with or without fever may receive granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) between days 28-42 days of azacitidine monotherapy or combination after discussion and agreement with the sponsor's project clinician (or designee). Patients who receive myeloid growth factors will not be included in assessment of neutrophil response.
Platelet transfusion	Permitted as medically necessary per institutional guidelines (eg, for platelets <10,000/µL in the absence of clinical bleeding); see Section 6.7.
Red blood cell transfusion	To be considered for all patients with anemia, especially those with hemoglobin values ≤8 g/dL; see Section 6.7.

G-CSF=granulocyte colony-stimulating factor, GM-CSF=granulocyte macrophage colony-stimulating factor.

6.6 Precautions and Restrictions

Concomitant medications and procedures that are excluded or must be used with caution are described in Sections 6.4 and 6.5, respectively.

Certain situations may warrant further caution, such as modifying the dose of study drug(s). Dose modification guidelines are provided in Section 6.3.

Refer to the package insert for VIDAZA USPI USPI) [35] or EU SmPC [66], for precautions and restrictions related to azacitidine use.

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

Female patients must meet 1 of the following:

- Postmenopausal (see Section 15.3) for at least 1 year before the Screening visit, or
- Surgically sterile, or

- If they are of childbearing potential, 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 study drug, or

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

- Female patients must agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

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

- Practice highly effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or

- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods 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 to not donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

6.7 Management of Clinical Events

6.7.1 Azacitidine

The most common adverse drug reactions for azacitidine are described in Section 1.6.1. For the single-agent azacitidine treatment arm, refer to the VIDAZA USPI [35] or EU SmPC SmPC) [66], as applicable, for details regarding the management of clinical events attributed to azacitidine.

6.7.2 Combination Pevonedistat Plus Azacitidine

Common AEs reported for patients receiving the combination of pevonedistat and azacitidine are listed in Section 1.6. Also see the most recent IB. For the Combination Pevonedistat Plus Azacitidine Arm, follow the guidance in the following subsections of this protocol.

Guidance for Clinical Assessment and Management of Hemodynamic Compromise

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

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

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

Guidance Management of Leukostasis

Pevonedistat treatment should be withheld for patients who develop symptoms of leukostasis (see Section 6.3.2.2). 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's project clinician (or designee). Azacitidine treatment may continue as clinically indicated.

Guidance for Management of 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.

6.8 Blinding and Unblinding

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

6.9 Description of Investigational Agents

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

6.9.1 Azacitidine

Azacitidine may be supplied by the site from commercial sources, depending on regional availability. Commercially available azacitidine is supplied as lyophilized powder in 100-mg single-use vials. Refer to the Study/Pharmacy Manual and the VIDAZA USPI [35] or EU SmPC [66], as applicable, for additional information regarding azacitidine.

6.9.2 Pevonedistat

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

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

Each Pevonedistat Concentrate for Solution for Infusion vial contains 50 mg Pevonedistat, as free base, formulated with the following excipients: citric acid (anhydrous), trisodium citrate dihydrate, Betadex Sulfobutyl Ether Sodium (Captisol®), and water for injection.

Details are available in the IB.

6.10 Preparation, Reconstitution, and Dispensation

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

Each Pevonedistat Concentrate for Solution for Infusion vial contains nominally 5 mL (50 mg) Pevonedistat, as free base. Using sterile technique, the appropriate volume of drug should be withdrawn from vial(s) and injected into a 250-mL IV bag containing a 5% dextrose solution. The bag must be gently inverted repeatedly to mix the contents. The prepared Pevonedistat IV bag must be used within 6 hours if stored at room temperature or discarded. Alternatively, the prepared IV bag is chemically stable and may be stored for up to 18 hours at 2°C to 8°C. After 18 hours of storage at 2°C to 8°C, the prepared IV bag must be used within 3 hours upon coming to room temperature or must be discarded.

The vial must not be shaken at any time during dose preparation.

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

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

Instructions for the preparation, reconstitution, and dispensation of azacitidine are provided in the VIDAZA USPI [35] or EU SmPC [66].

6.11 Packaging and Labeling

Pevonedistat Concentrate for Solution for Infusion will be provided in 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.

6.12 Storage, Handling, and Accountability

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

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

Details of the storage and handling of azacitidine are provided in the VIDAZA USPI [35] or EU SmPC [66].

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 Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the sponsor's project clinician for this study, the central laboratory and any additional clinical laboratories or vendors participating on the study may be found in the Study Manual. 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 Group Assignments

Patient eligibility will be established before randomization into the study as patients will not be permitted to re-enroll. Confirmation of patient eligibility by the sponsor's project clinician (or designee) following review and approval of a Patient Eligibility Checklist is required prior to randomization. A centralized randomization and stratification using an interactive web response system (IWRS) will be used. Patients will be randomized strictly sequentially at a center as they become eligible for randomization and will be stratified as detailed in Section 8.1.2. The study drug regimen must be initiated within 5 days of randomization on study. If a patient discontinues from the study, his/her randomization code will not be reused, and the patient will not be allowed to re-enter the study.

7.4 Study Procedures

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow, and in the Study and Laboratory Manuals. When applicable, specific visit windows for study procedures are provided in the footnotes to the study schedules.

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.

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

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

7.4.2 Inclusion/Exclusion Confirmation

During the screening process, a Patient Eligibility Checklist must be completed and submitted by the investigator for review and approval by the sponsor or designee prior to patient randomization. Completion of the eligibility checklist is necessary to verify that the patient has met all of the inclusion and exclusion criteria. Source documentation allows for independent verification that patient eligibility has been determined by the proper methodology. Unless specifically requested, additional source documentation does not need to be submitted with the checklist for the assessment of eligibility related to the other inclusion and exclusion criteria.

7.4.3 Patient Demographics

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

7.4.4 Medical History and IPSS-R Risk Categorization

During Screening, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's HR MDS or CMML or low-blast AML (see inclusion criteria 2 and 3, Section 5.1, for definitions), including an assessment of bone marrow morphology (see Section 7.4.20 for additional details on bone marrow sample collection and evaluation). Information regarding any prior therapy for HR MDS or CMML or low-blast AML, including start and stop dates of each therapeutic agent and response to therapy, will be collected in the eCRF. In addition, all blood transfusions related to HR MDS or CMML or low-blast AML that the patient received within 8 weeks prior to randomization will be recorded to document baseline transfusion dependence.

For patients with HR MDS or CMML (but not for patients with low-blast AML), screening assessments must include risk categorization (for patients both with HR MDS and with CMML) according to the IPSS-R [2]. Source documents supporting the prognostic risk category determination may be requested with the Patient Eligibility Checklist for review by the sponsor prior to randomization (see Section 7.4.2).

The IPSS-R Prognostic Score values based on specific criteria are provided in Table 7.a, and the IPSS-R cytogenetic risk groups are provided in Table 7.b. Cytogenetic risk groups and bone marrow blast percentages will be based upon results from the local laboratory, while clinical lab values (hemoglobin, platelets and ANC) should be from the central laboratory results. Criteria and score values from these tables are used to determine the overall risk category as listed in Table 7.c. These 3 tables have been adapted from:

www.mds-foundation.org/ipss-r-calculator/ (accessed 05 January 2015), based on Greenberg et al., 2012 [2].

Additional details and instructions for determining the prognostic risk category are provided in the Study Manual.

Table 7.a IPSS-R Prognostic Score Values

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

Source: Greenberg et al., 2012 [2].

BM=bone marrow; ANC=absolute neutrophil count.

(a) Patients with indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points (ie, intermediate) for determining overall Prognostic Risk Category/Score.

Table 7.b IPSS-R Cytogenetic Risk Groups

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

Sources: Greenberg et al., 2012 [2] and Schanz J et al., 2012 [71].

Table 7.c IPSS-R Prognostic Risk Categories/Scores

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

Source: Greenberg et al., 2012 [2].

7.4.5 Modified Charlson Comorbidity Index Assessment

Patients will be assessed during screening using the modified Charlson comorbidity index (refer to Section 15.7).

7.4.6 Physical Examination

A complete physical examination will be performed per standard of care at Screening and at the EOT visit. A symptom-directed physical examination will be completed per standard of care at the times specified in the Schedule of Events, and as clinically indicated.

7.4.7 Patient Height

Height will be measured only during Screening.

7.4.8 Patient Weight

Weight will be measured during Screening, within 3 days before Day 1 dosing in all cycles, and at the EOT visit. If the screening assessment was done within 3 days before Cycle 1 Day 1, an assessment at Cycle 1 Day 1 is not necessary.

The amount of study drug (pevonedistat and/or azacitidine, as applicable) to be administered will be based on BSA. BSA will be calculated using a standard formula (see example in Section 15.8) 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.

7.4.9 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed at the times specified in the Schedule of Events. Refer to Section 15.1 for the performance status grading scale.

7.4.10 Vital Signs

Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected at Screening, predose on Days 1, 3, and 5 on each treatment arm of each treatment cycle, at EOT, and as clinically indicated. Vital sign measurements will be taken with the patient in the supine or sitting position.

7.4.11 Electrocardiogram

A 12-lead ECG will be administered at the time points specified in the Schedule of Events. Additional ECGs may be performed as clinically indicated.

7.4.12 Chest X-ray

A chest X-ray will be performed during Screening. If a chest X-ray or chest CT scan was done within 2 months prior to randomization, the chest X-ray does not need to be done during Screening.

7.4.13 Enrollment

Enrollment is achieved when the patient is randomized onto study treatment.

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

7.4.14 Clinical Laboratory Evaluations

Handling and shipment of clinical laboratory samples will be outlined in the Laboratory Manuals.

Clinical laboratory evaluations will be performed by a central laboratory. The central laboratory results also should be used for determination of eligibility criteria by the sponsor's project clinical (or designee) before randomization. For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must still be sent to the central laboratory as well. Local laboratory evaluations may be done more frequently at the investigator's discretion, for instance management of anemia. Central laboratory results may not be available due to (but not limited to) the following reasons:

- Samples are not able to be analyzed by central laboratory (for various reasons).

- Laboratory-dependent decisions needed for patient treatment have to be made before the availability of central lab results.

In the instance when a local laboratory is used and central laboratory results are subsequently available, a retrospective review will be completed by the sponsor's project clinician (or designee) to determine any significant difference between those results. In the event of a significant difference, the sponsor may provide further advice to the clinical site.

Coagulation testing (prothrombin time and activated partial thromboplastin time) will be done at Screening and sent to the central laboratory.

Blood samples for analysis of the following hematology parameters will be obtained as specified in the Schedule of Events:

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential, including percent circulating blasts
- Neutrophils (ANC); ANC will be calculated from the leukocyte count with differential count; see Section 15.9.

Blood samples for analysis of reticulocyte counts and ferritin levels will be obtained as specified in the Schedule of Events and sent to the central laboratory.

Blood samples for analysis of the following serum chemistry parameters will be obtained as specified in the Schedule of Events:

Complete Serum Chemistry Panel

- BUN
- Creatinine
- Bilirubin (total)
- Direct bilirubin
- Urate
- Lactate dehydrogenase (LDH)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium

Select Serum Chemistry Panel

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

Blood phosphate tests will be performed on Day 5 of each treatment cycle or the day on which the third dose of pevonedistat is given if it is not Day 5 (to be performed by the central laboratory).

Urine samples for urinalysis will be obtained as specified in the Schedule of Events and sent to the central laboratory.

Urinalysis with Microscopic Analysis

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

7.4.15 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening. A pregnancy test must also be performed for women of childbearing potential at every cycle (typically performed on Day 1 of the cycle; however, if a serum pregnancy test is used, this may be performed up to 3 days before Day 1) with negative results available before the first dose is administered in that cycle. A pregnancy test will also be performed for women of childbearing potential at the EOT visit to exceed the end of systemic exposure, which is 2 days for pevonedistat.

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

7.4.16 Health-Related Quality of Life Questionnaires

To compare the impact of treatment between the 2 treatment arms in this study, patient-reported HRQOL will be assessed by 3 instruments: EORTC-QLQ-C30 and EQ-5D-5L (all patients) and QOL-E (US patients only). During study treatment and EFS follow-up periods for HR MDS/CMML patients or response follow-up for patients with low-blast AML, patient-reported HRQOL will be collected from all patients as indicated in the Schedule of Events.

The patient should be given the paper version of the questionnaires to be completed at the scheduled visit before other clinical assessments are conducted. The questionnaires should be completed in the language most familiar to the respondent, at the scheduled visit, before the patient sees the investigator for clinical assessments. The patient should be given

sufficient space and time to complete the questionnaires. The patient should complete the questionnaires on their own without any assistance from site staff or a caregiver. The questionnaires are intended to be self-reported and should not be interviewer administered.

The study coordinator should check the questionnaire for completeness and encourage the patient to complete any missing responses. Detailed instructions relating to the administrative procedures of the questionnaires will be provided to the sites. Patient's refusal to complete all or any part of a questionnaire should be documented in the eCRF.

EORTC-QLQ-C30

The EORTC-QLQ-C30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 individual items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Most of the 30 items have 4 response levels (not at all, a little, quite a bit, and very much), with 2 questions relying on a 7-point numeric rating scale. Raw scores are converted into scale scores ranging from 0 to 100. For the functional scales and the global health status scale, higher scores represent better HRQOL; whereas for the symptom scales lower scores represent better HRQOL. All items in this questionnaire relate to a recall period of 1 week.

QOL-E

The QOL-E assesses HRQOL in 5 general domains (general well-being, physical well-being, functional well-being, social well-being, sexual well-being) and disease-related issues, with a recall period of 1 week with the exception of 1 general health item (1 month). A higher score indicates a better HRQOL for that domain. The QOL-E will be administered to American English-speaking patients in the US only.

EQ-5D-5L

The EQ-5D-5L is a self-administered preference-based measure of health status suitable for calculating QALYs to inform economic evaluations. EQ-5D-5L includes 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and 5 response levels for each domain (no problems, slight problems, moderate problems, severe problems, and extreme problems). Patients are asked to indicate their health state by selecting the most appropriate level of severity on each of the 5 dimensions. Patient responses to the 5 dimensions of the EQ-5D-5L represent the patient's health state that is transformed to a

utility score using preferably country-specific value sets for the calculation of QALYs that are used to inform economic evaluations. There is also a visual analogue scale used by respondents to rate their health on a scale from best (100) to worst (0).

7.4.17 Hospitalization Assessment

During study treatment and EFS follow-up periods for HR MDS/CMML patients or response follow-up for patients with low-blast AML, all hospitalizations since the previous assessment will be collected from all patients as indicated in the Schedule of Events. Examples of data to be collected are number and duration of inpatient hospitalizations, location of admission (eg, ICU, hospital floor bed), and reason(s) for admission and primary diagnosis at discharge. Transfusion data will also be collected. For example, the number of patients who received pRBCs and number of units received, number of patients who received a platelet transfusion and number of units received, and location of transfusion (inpatient vs outpatient).

7.4.18 Pharmacokinetic Measurements

Blood samples (approximately 3 mL each) for the determination of pevonedistat (and its metabolites, if appropriate) plasma concentrations will be collected from all patients in the Combination Pevonedistat Plus Azacitidine Arm at the time points indicated in the Schedule of Events. The exact date and time of each sample collection, as well as the actual start and stop times of the study drug administration, should be recorded accurately, and particular care should be 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 to a patient's IV infusion. In the case that only a single arm is available, blood should be drawn as distal to the site of 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.

7.4.19 CCI

CCI

CCI

[redacted]

7.4.20 Bone Marrow Aspirate and Biopsy Collection and Analysis

Bone Marrow Sample Collection for Disease Assessment

Bone marrow aspirates and biopsies will be required during the study as detailed in the Bone Marrow Collection and Assessment Schedule.

In addition, a bone marrow assessment will be performed for disease assessment at relapse (or suspected relapse) or PD, and if otherwise clinically indicated (eg, major changes in the patient's underlying hematological disease are suspected). Note that the detection of circulating blasts is not by itself a sufficient criterion for relapse, but should trigger a bone marrow examination to determine whether a relapse has occurred. Other examples of triggers for ad hoc bone marrow examination may include a 50% reduction from maximum remission/response in granulocytes or platelets or a reduction in hemoglobin by ≥2 g/dL that is not considered drug related (eg, do not recover), or the hematologic values prompt new or more frequent transfusion support than the patient's baseline status.

A bone marrow biopsy (in addition to bone marrow aspirate) is required only at Screening to confirm the diagnosis. However, a bone marrow biopsy may be collected with bone marrow aspirate in accordance with institutional guidelines. If a biopsy was done within 28 days prior to enrollment, this archival biopsy may be used and does not need to be repeated. If

bone marrow biopsy is not collected routinely per country/institutional guidelines, it is not required.

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

- Determine blast count on aspirate samples: Samples will be evaluated locally for blast count per institutional standard practice to inform disease burden assessment. Samples will also be sent to a central laboratory for confirmation of bone marrow blast count.

- Analyze cytogenetics for IPSS-R score determination and disease response assessment for patients with HR MDS and CMML. CCI [redacted] A portion of the bone marrow aspirate sample at Screening will also be sent to each site's preferred cytogenetic laboratory for cytogenetics assessment according to institutional guidelines (by karyotype and/or fluorescence in situ hybridization [FISH]). Chromosomal abnormalities and translocations that are routinely assessed for the diagnosis of MDS and AML and are included in the IPSS-R Prognostic Risk Score include, for example, trisomy 8, del(5)q, monosomy 7, del(20)(q), +6, +13, +21, t(5;12)(q33;p13), other 12p changes, t(3;5)(q25;q34), inv(3)(q21q26), rearrangements involving 1q, 11q23, 17p-/-17 and X chromosome.

CCI [redacted]

The bone marrow pathology reports, cytogenetics reports, CCI [redacted] from the local laboratories will be submitted to the sponsor.

In addition to submitting bone marrow samples to the **local laboratory** (as per institutional guidelines), the samples should be submitted to the **central laboratory,** as follows:

- Whenever a bone marrow *aspirate* is collected, 2 to 3 unstained aspirate smears (either uncharged or charged slides) should be submitted to the central laboratory.

- Whenever a bone marrow *biopsy* is collected, it should be submitted to the central laboratory.

Acceptable bone marrow biopsy samples in order of preference are as follows:

1. 5 unstained slides (charged slides) from core biopsy specimen 3 to 5 microns thick.
2. Formalin-fixed paraffin embedded tissue block.
3. Core biopsy in formalin-filled container.

These bone marrow samples that are being sent to the **central laboratory** are for:

- Quality control evaluation of blast count assessments: Bone marrow samples will also be sent to a central laboratory, in addition to those sent for local laboratory examination, for evaluation of blast count. The procedure for handling, preparation and shipment of samples is outlined in the Study Manual. Samples will be evaluated by the central laboratory at each time point (including any unscheduled samples) and results will be reported to the sponsor. This evaluation will not be a real-time confirmation of progression, and results will not be routinely available to the clinical sites. Clinical decisions will be based on local laboratory blast count results. Discrepancies between local study site results and central laboratory results will be reviewed by the sponsor.

Following Cycle 4, bone marrow collection will be performed only as clinically indicated in patients who achieve CR. In all other patients who do not achieve CR, bone marrow assessments will be performed after completion of every third treatment cycle. Additional bone marrow aspirates may be performed if warranted by changes in peripheral blood counts.

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

CCI

CCI

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

7.4.21 Disease Assessment

Formal disease assessments for study endpoints will be determined based on local bone marrow aspirate blast counts and transfusions, and central lab data (local lab data may be used for time-sensitive clinical decisions). The investigator's assessment of disease status will be entered into the eCRF for each time point.

Transformation to AML may occur in both MDS and CMML. In this study, transformation to AML is defined, according to WHO Classification [72] as a patient having >20% blasts in the blood or marrow AND increase of blast count by 50%. To illustrate:

- For patients with 5% to 10% blasts pretreatment: a >50% increase to >10% blasts constitutes progression of MDS.
- For patients with 10% to 20% blasts pretreatment: a >50% increase to >20% blasts constitutes transformation to AML.

Note: The principal investigator should make all efforts to perform the disease assessment by a bone marrow examination. However, in the exceptional circumstance that it is not possible to have a bone marrow examination from patients for disease assessment, transformation to AML will also be defined as >20% blasts in peripheral blood AND an increase of blast count by 50% from pretreatment.

Note that, according to the WHO Classification [72]:

> The blast percentage and assessment of degree of maturation and dysplastic abnormalities in the neoplastic cells should be determined, if possible, from a 200-cell leukocyte differential performed on a peripheral blood smear and a 500-cell differential performed on marrow aspirate smears stained with Wright Giemsa or May-Grunwald Giemsa. The blast percentage should be correlated with an estimate of the blast count from the marrow biopsy section. In addition to myeloblasts, the monoblasts and promonocytes in acute monoblastic/monocytic and acute and chronic myelomonocytic leukemia and the megakaryoblasts in acute megakaryoblastic leukemia are considered as 'blast equivalents' when the requisite percentage of blasts is calculated for the diagnosis of AML.

As defined in Table 7.d and Table 7.e, additional assessment(s) of disease response for patients with MDS or CMML are based on the criteria outlined in the Modified IWG Response Criteria for MDS [3]; and additional assessments of disease response for patients with low-blast AML are based on 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 (Table 7.f.).

Note that standard MDS guidelines [33] also recommend treatment for 6 cycles without altering dose or frequency of azacitidine regardless of cytopenias. Therefore, in this study, patients with HR MDS or CMML may be allowed to continue study treatment (either treatment arm), even if they meet the criteria for progressive disease based only on bone marrow blast counts (without AML transformation), if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment.

Investigators should note that some AML 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 relapsed/refractory 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 declined. 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, patients with low-blast AML, in this study, also may be allowed to continue study treatment (either treatment arm), even if they meet the criteria for progressive disease based only on bone marrow blast counts, if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment. If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study.

A minimum of 6 cycles of treatment is strongly encouraged. In the event that early removal from the study is being considered for toxicity or stable disease, contact the sponsor's project clinician (or designee) to discuss before the patient is removed from the study.

Table 7.d Response Criteria for Altering Natural History of MDS and CMML

Category	Response Criteria
Complete remission (CR)	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines (a) Persistent dysplasia will be noted (a) Peripheral blood (b) Hgb ≥11 g/dL Platelets $\geq 100 \times 10^9$/L Neutrophils $\geq 1.0 \times 10^9$/L Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥50% over pretreatment but still >5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment Peripheral blood: 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 wks If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study.
Failure	Death during treatment or PD (as defined below), or progression to AML or a more advanced MDS or CMML FAB/WHO subtype than pretreatment

Table 7.d Response Criteria for Altering Natural History of MDS and CMML

Category	Response Criteria
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
Cytogenic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality
Progressive disease (PD)	**Note: Transient cytopenias during chemotherapy courses should not be considered PD, as long as they recover to the previous levels. Progression based on blood values should not be considered at all until after the post-Cycle 4 marrow draw.** If a patient has ≥50% increase in blast count from pretreatment (without AML transformation) but is still deriving benefit from this treatment (eg, improvement in peripheral blood counts), the patient may continue on study as agreed by the investigator and the sponsor's project clinician (or designee). For patients with: Less than 5% blasts: ≥50% increase in blasts to >5% blasts 5% - 10% blasts: ≥50% increase to >10% blasts 10% - 20% blasts: ≥50% increase to >20% blasts 20% - 30% blasts: see Table 7.f "Response Criteria for AML" Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥2 g/dL New transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: PD or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

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

AML=acute myelogenous leukemia, CMML=chronic myelomonocytic leukemia, CR=complete remission, DFS=disease-free survival, FAB=French-American-British, Hgb=hemoglobin, HI=hematologic improvement, MDS=myelodysplastic syndromes, PD=progressive disease, PFS=progression-free survival, 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). 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.e Response Criteria for Hematologic Improvement for MDS and CMML

Hematologic Improvement (a)	Response criteria (responses must be at least 8 weeks in duration)
Erythroid response (pretreatment, <11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wks compared with the pretreatment transfusion number in the previous 8 wks. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment, $<100\times10^9$/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

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

The revised recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia will be used for assessment of disease response [4]. Investigators are encouraged to consult the reference for more detailed explanation of response criteria.

Table 7.f Response Criteria for AML

Category	Response Criteria
Morphologic Complete Remission (CR)	A CR designation requires that the patient achieve the morphologic leukemia-free state and have an ANC of more than 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 Complete Remission with Incomplete Blood Count Recovery (CRi)	After chemotherapy, some patients fulfill all of the criteria for CR except for residual neutropenia (< 1,000/µL) or thrombocytopenia (< 100,000/µL).
CCI	[redacted]

Table 7.f Response Criteria for AML

Category	Response Criteria
Partial Remission (PR)	This designation requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. Thus, if the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pretreatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%. A repeat bone marrow aspiration after several weeks may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration. A value of ≤ 5% blasts may also be considered a PR if Auer rods are present.
Progressive disease (PD)	Because the IWG criteria for AML do not provide a standardized definition for PD, [4] in this protocol, PD is defined as one of the following: • > 50% increase in bone marrow blasts from baseline value to > 30% blasts • > 50% increase in circulating blasts from baseline value to > 30% blasts in peripheral blood (in the exceptional case when bone marrow examination is not possible) • Development of biopsy-proven extramedullary disease, or new sites of extramedullary leukemia
Relapse after CR	Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy). In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration.

7.4.22 Adverse Events

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

7.4.23 Concomitant Medications and Procedures

All concomitant medications and procedures (excluding transfusions) will be recorded from the time of the first dose of any study drug through 30 days after the last dose of any study drug. RBC and platelet transfusions will be recorded from 8 weeks before randomization through 30 days after the last dose of any study drug. See Section 6.4 and Section 6.5 for additional details regarding excluded and permitted concomitant medications and procedures.

7.5 Completion of Treatment

A patient has completed the treatment if they discontinue treatment for any of the reasons listed in Section 7.7. Note that PD includes transformation to AML, relapse after CR for patients with low-blast AML, or other PD as defined in Section 7.4.21.

As detailed in Section 1.3, some patients in Study C15003 (single-agent pevonedistat in patients with relapsed/refractory AML) derived clinical benefit from continuing study treatment despite changes in their bone marrow blast counts. Standard MDS guidelines [36] also recommend treatment for 6 cycles without altering dose or frequency of azacitidine regardless of cytopenias. **Therefore, in this study, patients may be allowed to continue study treatment (either treatment arm), even if they meet the criteria for PD based only on bone marrow blast counts (without AML transformation), if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study. If a patient has ≥50% increase in blast count from pretreatment (without AML transformation), but is still deriving benefit, the patient may continue on study as agreed by the investigator and the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment.**

A minimum of 6 cycles of treatment is strongly encouraged. In the event that early removal from the study is being considered for toxicity or stable disease, contact the sponsor's project clinician (or designee) to discuss before the patient is removed from the study.

Patients will attend an EOT visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner; refer to the Schedule of Events for EOT visit assessments. All patients will then continue to be followed as specified in the Schedule of Events:

- Patients who have not transformed to AML (for patients with HR MDS or CMML at study entry) or who have not progressed (patients with low-blast AML at study entry) at the time of the EOT visit will enter EFS Follow-up. If a patient with HR MDS or CMML at study entry subsequently transforms to AML (as defined in Section 7.4.21) or initiates subsequent therapy during the EFS Follow-up period, the

patient will then enter OS Follow-up. If a patient with low-blast AML subsequently progresses or relapses (as defined in Section 7.4.21) or initiates subsequent therapy during the EFS Follow-up period, the patient will then enter OS Follow-up period.

- Patients with HR MDS or CMML at study entry that has transformed to AML and patients with low-blast AML at study entry who have experienced progressive disease or relapse after CR at the time of the EOT visit will enter OS Follow-up immediately.

7.6 Completion of Study

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

7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement

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

- Adverse event
- Protocol violation
- Progressive disease

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

- Disease relapse
- Subsequent anti-cancer therapy
- 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 EOT visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who are randomized to a treatment arm but do not receive study drug for any reason will not 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
- Other

Millennium or their designee must be notified in writing if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records. The investigators will make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. If a patient withdraws from study treatment, every attempt should be made to follow the patient until death or administrative study closure. Final treatment assessments will be performed before any other therapeutic intervention if possible. Additionally, any planned alternative treatments should be documented on the patient's medical records and CRF.

7.9 Study Compliance

Study drug will be administered 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 administration.

7.10 Posttreatment Follow-up Assessments (Event-Free Survival, Response Follow-up, and Overall Survival)

Patients who discontinue study treatment will complete the EOT visit 30 days (+10) after the last dose of study drug(s) or before the start of subsequent antineoplastic therapy if that occurs sooner. After the EOT visit, patients will continue to be followed for EFS (for patients with HR MDS/CMML), response follow-up (for patients with AML), and OS endpoints as detailed in the Schedule of Events. All subsequent therapies for MDS, CMML, and/or AML (as applicable) will be recorded, regardless if they are initiated before or after PD or transformation to AML.

NOTE: Related SAEs must be reported to Millennium Department of Pharmacovigilance or designee. This includes deaths that the Investigator considers related to study drug that occur during the posttreatment follow up. Refer to Section 10 for details regarding definitions, documentation, and reporting of SAEs.

7.11 Posttrial Access

7.11.1 Posttrial Access

If an open-label, rollover, posttrial access (PTA) study should become an option and the investigator and the sponsor agree that a patient would derive benefit from continued treatment or would be harmed without continued access to the medication, the patient may be given the opportunity to enroll. The patient would then be able to continue receive pevonedistat (if randomized to the combination arm).

7.11.2 Duration of PTA

In the event of a rollover PTA study, continued access to pevonedistat for participants will be terminated for those individuals who no longer benefit from treatment (eg, their disease has progressed or treatment is no longer tolerable), the benefit-risk no longer favors the individual, an appropriate alternative therapy becomes available, or pevonedistat becomes available either commercially or via another access mechanism. PTA may be terminated in a country or geographical region where the development of pevonedistat has been suspended or stopped by the sponsor, or pevonedistat can no longer be supplied.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

A formal statistical analysis plan (SAP) will be developed and finalized before database lock. This plan will outline all data handling conventions and specify all statistical methods to be used for safety and efficacy data analysis.

Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

8.1.1 Determination of Sample Size

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

8.1.2 Randomization and Stratification

Patients will be randomized to receive the combination of pevonedistat and azacitidine or azacitidine alone in a 1:1 ratio, stratified into 4 categories: low-blast AML, IPSS-R risk groups of very high, high, or intermediate for MDS/CMML [2]. (Note that patients with indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points, ie, intermediate, for determining overall Prognostic Risk Category/Score; see Section 7.4.4).

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: The safety population is defined as all patients who receive at least 1 dose of pevonedistat plus azacitidine or azacitidine alone. Patients will be analyzed according to the actual treatment they received. Patients who received any dose of pevonedistat will be included in the Combination Pevonedistat Plus Azacitidine Arm, and patients who did not receive any dose of pevonedistat, but received at least 1 dose of azacitidine, will be included in the Single-Agent Azacitidine Arm, regardless of their randomized treatment.

- Intent-to-treat (ITT) population: The ITT population is defined as all patients who are randomized. Patients in this population will be analyzed according to the treatment they were randomized to receive, regardless of any dosing errors.

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

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. 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. Details on any sensitivity analyses and data handling details regarding issues such as missing data will be discussed in the SAP.

8.1.5 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively, including gender, age, race, weight, height, and other parameters as appropriate. No inferential statistics will be carried out.

Throughout this study, baseline assessments are defined as those performed at the closest time before the start of study drug administration.

8.1.6 Efficacy Analysis

8.1.6.1 General Methodology

Summary tabulations will be presented by treatment group and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable) will also be provided, along with their 2-sided 95% CIs for time to event data.

All efficacy primary analyses will be based on investigator assessments. Any sensitivity analysis will be specified in the SAP.

8.1.6.2 Analyses of Primary Efficacy Endpoints

The analysis of the primary efficacy endpoint, OS, will be based on HR MDS/CMML patients and the ITT population separately.

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

OS will be calculated from date of randomization to the date of patient death due to any cause. Patients without documented death at the time of the analysis will be censored at the date that the patient was last known to be alive. Unstratified log-rank test will be used to compare OS between the 2 treatment arms. Hazard ratios, along with the 2-sided 95% CIs, will be estimated using the unadjusted, unstratified Cox model. The proportional hazard assumptions will be examined and sensitivity analysis will be conducted if appropriate. Kaplan-Meier curves and Kaplan-Meier medians (if estimable), together with the 95% CIs, will be calculated for each treatment group.

8.1.6.3 Analyses of Secondary Efficacy Endpoints

If the secondary efficacy endpoint is response related, such as CR, the response-evaluable population of patients with HR MDS/CMML, patients with low-blast AML, and the overall patient population will be used separately, if appropriate. Duration of the response-related endpoint will be analyzed based on the corresponding responders; otherwise, the analysis will be based on HR MDS/CMML patients and the ITT population separately.

For patients with low-blast AML, composite CR + CRi, CR as well as CRi will be analyzed.

Refer to Section 7.4.21 for response definitions (eg, complete remission, transformation to AML, PD).

EFS

The analysis of EFS, will be based on patients with HR MDS/CMML and the ITT population separately.

For patients with HR MDS/CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death. EFS is defined as the time from randomization to the occurrence of an event. Unstratified log-rank test will be used to compare EFS between the 2 arms. The hazard ratios along with the 2-sided 95% CIs will be estimated using the unadjusted, unstratified Cox model. The proportional hazard assumptions will be examined and sensitivity analysis will be conducted if appropriate. The Kaplan-Meier survival curves and Kaplan Meier medians (if estimable), along with the 95% CIs, will also be provided for each treatment group.

Six-Month and One-Year Survival Rate

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

Time to AML Transformation

Time to AML transformation is defined as time from randomization to documented AML transformation. This definition only applies to patients with HR MDS and CMML, so this analysis will only be carried out in this subgroup. Patients who died before progression to AML will be censored. Unstratified log-rank test will be used to compare time to AML transformation between the 2 arms. Hazard ratio and its 2-sided 95% CI will be calculated using the unstratified Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the 95% CIs, will be calculated for each treatment group.

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

CR/CR + PR (composite CR + PR for patients with low-blast AML)/overall response/CR (not including CRi) in low-blast AML calculations will be based on the response-evaluable population of patients overall, the response-evaluable patients with HR MDS/CMML, and the response-evaluable patients with low-blast AML, if appropriate.

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

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

The number and percentage of patients who achieved CR/CR + PR (composite CR + PR for low-blast AML)/overall response (CR + PR + HI for patients with HR MDS/CMML, composite CR + PR for patients with low-blast AML)/CR (not including CRi) in low-blast AML by Cycle 4, respectively, will be summarized by treatment group. CR rate/CR + PR (composite CR + PR for patients with low-blast AML) rate/overall response rate/CR rate (not including CRi) in low-blast AML by Cycle 4 between the 2 treatment arms, respectively, will be compared using the unstratified CMH chi-square test. The relative risk with its 2-sided 95% CI will be calculated. The absolute rate difference will be provided with its 95% CI.

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

Calculations of duration of responses will be based on responders from the overall patient population, responders from patients with HR MDS/CMML, and responders from patients with low-blast AML, if appropriate.

Duration of CR/CR + PR/overall response (CR + PR + HI for patients with HR MDS/CMML, CR + CRi + PR for patients with low-blast AML)/CR (not including CRi) in low-blast AML, respectively, will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates.

Time to First CR or PR

Analysis of time to first CR (composite CR for patients with low-blast AML) or PR will be based on the response-evaluable patients with HR MDS/CMML and the response-evaluable population for the overall patient population separately.

Time to first CR or PR is defined as time from randomization to first documented CR or PR, whichever occurs first. Unstratified log-rank test will be used to compare time to first CR or PR between the 2 arms. Hazard ratio and its 2-sided 95% CI will be calculated using the

unstratified Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the 95% CIs, will be calculated for each treatment group.

Time to Subsequent Therapy

Analysis of time to subsequent therapy will be based on patients with HR MDS/CMML and the ITT population separately.

Time to subsequent therapy is defined as time from randomization to the date of the first subsequent therapy. Subsequent therapy is defined as agent(s) with antileukemic/anti-MDS activity (eg, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.

Unstratified log-rank test will be used to compare time to subsequent therapy between the 2 arms. Hazard ratio and its 2-sided 95% CIs will be calculated using unstratified Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the 95% CIs will be calculated for each treatment group.

Rate of Transfusion Independence

Analysis of RBCs and platelet-transfusion independence will be based on patients with HR MDS/CMML and the ITT population separately.

A patient is defined as RBC or platelet-transfusion independent if he/she receives no RBC or platelet transfusions for a period of at least 8 weeks [13,73]. Rate of transfusion independence is defined as number of patients who become transfusion independent divided by the number of patients who are transfusion dependent at Baseline. The number of patients who are transfusion dependent/independent at Baseline and post Baseline, as well as rate of transfusion independence, will be summarized by treatment group. Rate of transfusion independence between the 2 treatment arms will be compared using unstratified CMH test. The relative risk with its 2-sided 95% CIs will be provided.

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

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

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

Time to PD, Relapse, or Death

Analysis of time to PD, relapse, or death will be based on patients with HR MDS/CMML and the ITT population separately.

Time to PD, relapse, or death is defined as the time from randomization until disease progression, or relapse, or death due to any cause, whichever occurs first. Unstratified log-rank test will be used for comparison between the 2 arms. The hazard ratios along with the 2-sided 95% CIs will be estimated using the unadjusted unstratified Cox model. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), along with the 95% CIs, will also be provided for each treatment group.

8.1.7 Analyses of Health-related Quality of Life

Analyses of HRQOL data for EORTC-QLQ-C30 and EQ-5D-5L will be performed based on patients with HR MDS/CMML and the ITT population separately; and for QOL-E data, the American English-speaking US patient population only will be used.

The PRO analysis will be performed based on subscale scores from EORTC-QLQ-C30 and QOL-E. The actual value and change from baseline of the subscale scores for EORTC-QLQ-C30 and QOL-E will be summarized using descriptive statistics by treatment group over time. The EORTC-QLQ-C30 and QOL-E subscale scores will also be analyzed using linear mixed models by incorporating the measurements across different time points. Data from the EQ-5D-5L will be assessed using descriptive statistics by treatment group over time.

8.1.8 Pharmacokinetics/Pharmacodynamics[CCI]

Pharmacokinetic Analysis

Individual pevonedistat plasma concentration-time data collected in this study will be listed.

Data will be pooled to describe the population PK of pevonedistat. As data permit, a nonlinear mixed effects modeling approach (NONMEM software) will be used to assess pevonedistat exposure in patients who receive the combination of pevonedistat and azacitidine. As appropriate, historical data may be used in this analysis to increase the

robustness of the model and precision of estimated PK parameters and compare with single- agent pevonedistat data. Details of the modeling approach will be provided in a separate analysis plan, and the results of these analyses will be reported separately.

CCI

8.1.9 Safety Analysis

Safety population will be used for all safety analyses.

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

All treatment-emergent adverse events (TEAEs) will be tabulated. TEAEs are AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of any study drug. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC), high-level term (HLT), and preferred term (PT) and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Treatment-emergent drug-related Grade 3, 4, and 5 AEs (presented by grade and overall).
- Treatment-emergent Grade 3, 4, and 5 AEs (presented by grade and overall).
- TEAEs resulting in study drug discontinuation.
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- Treatment-emergent SAEs.

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 grade from Baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the safety profile of pevonedistat plus azacitidine.

Baseline and change from baseline ECOG performance status will be summarized.

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

platelet) transfusions (which will be reported on an eCRF) will also be reviewed to determine transfusion dependence or independence, as detailed in Section 8.1.6.3.

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

Electrocardiogram Analysis

Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time point, including any unscheduled measurements.

8.1.10 Interim Analysis

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

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

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

9. STUDY COMMITTEES

9.1 Millennium Safety Monitoring

Safety data will be reviewed and assessed periodically by a Global Pharmacovigilance Safety Team and a Safety Management Committee throughout the conduct of the study. These reviews will include a Global Safety Lead from the study team, as well as other representation from the Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, and Clinical Operations departments at Millennium.

9.2 Independent Data Monitoring Committee

An IDMC will review safety and efficacy data at the first IA and safety and efficacy data at the second IA. The IDMC will provide a recommendation regarding study continuation based on the overall analysis of safety and efficacy parameters and if it is deemed unacceptable, the study will stop. In the event that the study is terminated early based on an IDMC recommendation, Millennium will notify the appropriate regulatory authorities. Additionally, the IDMC will periodically review data per 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

Adverse event (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

Serious AE (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 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 [68]. Clarification should be made between a serious AE (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 white blood cell 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

CCI

[redacted]

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial 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 [68]. 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 the first dose of any study drug through 30 days after administration of the last dose of any 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 the EOT visit, 30 (+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.

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

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

11. 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 that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

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

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** (DLLS) and report the complaint. **The contact information is as follows**:

Call center	Phone number	E-mail	Fax
DLSS	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo @takeda.com	1-800-881-6092

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 [redacted] (refer to Section 10.2).

11.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the IECs in all member states where the study is being carried out that the study has ended, as well as the competent authorities, where required.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in 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 enter 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.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

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 pevonedistat 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 pevonedistat 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-2001 Amendment 04: A Phase 2, Randomized, Controlled, Open-Label, Clinical Study of the Efficacy and Safety of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Low-Blast Acute Myelogenous Leukemia.

I agree to conduct the study as detailed herein and in compliance with International Conference on 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)

14. REFERENCES

1. Armand P, Kim HT, DeAngelo DJ, Ho VT, Cutler CS, Stone RM, et al. Impact of cytogenetics on outcome of de novo and therapy-related AML and MDS after allogeneic transplantation. Biol Blood Marrow Transplant 2007;13(6):655-64.
2. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65.
3. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108(2):419-25.
4. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21(24):4642-9.
5. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51(2):189-99.
6. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114(5):937-51.
7. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391-405.
8. Sekeres MA, Gerds AT. Established and novel agents for myelodysplastic syndromes. ASH Education Program Book 2014;2014(1):82-9.
9. Zeidan AM, Linhares Y, Gore SD. Current therapy of myelodysplastic syndromes. Blood Rev 2013;27(5):243-59.
10. Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. J Clin Oncol 2014;32(24):2541-52.
11. Sekeres MA, Cutler C. How we treat higher-risk myelodysplastic syndromes. Blood 2014;123(6):829-36.
12. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355(14):1456-65.
13. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10(3):223-32.

14. Kantarjian H, O'Brien S, Cortes J, Wierda W, Faderl S, Garcia-Manero G, et al. Therapeutic advances in leukemia and myelodysplastic syndrome over the past 40 years. Cancer 2008;113(7 Suppl):1933-52.

15. Mufti GJ, Potter V. Myelodysplastic syndromes: who and when in the course of disease to transplant. Hematology 2012;2012:49-55.

16. Luger SM, Ringden O, Zhang MJ, Perez WS, Bishop MR, Bornhauser M, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. Bone Marrow Transplant 2012;47(2):203-11.

17. Sekeres MA, Schoonen WM, Kantarjian H, List A, Fryzek J, Paquette R, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. J Natl Cancer Inst 2008;100(21):1542-51.

18. Sekeres MA, Tiu RV, Komrokji R, Lancet J, Advani AS, Afable M, et al. Phase 2 study of the lenalidomide and azacitidine combination in patients with higher-risk myelodysplastic syndromes. Blood 2012;120(25):4945-51.

19. Prebet T, Sun Z, Figueroa ME, Ketterling R, Melnick A, Greenberg PL, et al. Prolonged administration of azacitidine with or without entinostat for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: results of the US Leukemia Intergroup trial E1905. J Clin Oncol 2014;32(12):1242-8.

20. Zandberg DP, Huang TY, Ke X, Baer MR, Gore SD, Smith SW, et al. Treatment and outcomes for chronic myelomonocytic leukemia compared to myelodysplastic syndromes in older adults. Haematologica 2013;98(4):584-90.

21. Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th Edition, Vol. 2. Lyon: IARC Press; 2008.

22. Emanuel PD. Mixed myeloproliferative and myelodysplastic disorders. Current Hematologic Malignancy Reports 2007;2(1):9-12.

23. Germing U, Kundgen A, Gattermann N. Risk assessment in chronic myelomonocytic leukemia (CMML). Leuk Lymphoma 2004;45(7):1311-8.

24. Onida F, Kantarjian HM, Smith TL, Ball G, Keating MJ, Estey EH, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. Blood 2002;99(3):840-9.

25. Parikh SA, Tefferi A. Chronic myelomonocytic leukemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol 2012;87(6):610-9.

26. Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Della Porta MG, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood 2013;121(15):3005-15.

27. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002;20(10):2429-40.

28. Soucy TA, Smith PG, Milhollen MA, Berger AJ, Gavin JM, Adhikari S, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. Nature 2009;458:732-6.

29. Lin JJ, Milhollen MA, Smith PG, Narayanan U, Dutta A. NEDD8-targeting drug MLN4924 elicits DNA rereplication by stabilizing Cdt1 in S phase, triggering checkpoint activation, apoptosis, and senescence in cancer cells. Cancer Res 2010;70(24):10310-20.

30. Milhollen MA, Narayanan U, Soucy TA, Veiby PO, Smith PG, Amidon B. Inhibition of NEDD8-activating enzyme induces rereplication and apoptosis in human tumor cells consistent with deregulating CDT1 turnover. Cancer Res 2011;71(8):3042-51.

31. Swords RT, Erba HP, DeAngelo DJ, Bixby DL, Altman JK, Maris M, et al. Pevonedistat (MLN4924), a First-in-Class NEDD8-activating enzyme inhibitor, in patients with acute myeloid leukaemia and myelodysplastic syndromes: a phase 1 study. Br J Haematol 2015;169(4):534-43.

32. Swords RT, Savona MR, Maris MB, Erba HP, Berdeja JG, Foran JM, et al. Pevonedistat (MLN4924), an investigational, first-in-class NAE inhibitor, in combination with azacitidine in elderly patients with acute myeloid leukemia (AML) considered unfit for conventional chemotherapy: Updated results from the phase 1 C15009 trial. 2014 Annual Meeting of the American Society of Hematology (ASH); 06-09 December 2014; San Francisco, CA.

33. Swords R, Erba H, DeAngelo D, Smith P, Pickard M, Dezube B, et al. The Novel, Investigational NEDD8-Activating Enzyme Inhibitor MLN4924 In Adult Patients with Acute Myeloid Leukemia (AML) or High-Grade Myelodysplastic Syndromes (MDS): A Phase 1 Study. Blood (ASH Annual Meeting Abstracts) 2010;116(21):abstr 658.

34. García R, De Miguel D, Bargay J, Bernal T, Gonzalez J, Tormo M, et al. Effectiveness of Various Dosage Regimens of Azacitidine In Patients with Myelodysplastic Syndromes: Safety and Efficacy Final Data From the Spanish Azacitidine Compassionate Use Registry. Blood (ASH Annual Meeting Abstracts) 2010;116(21):abstr 1853.

35. VIDAZA (azacitidine for injection) for SC or IV use [package insert]. Summit, NJ: Celgene Corporation, 2014.

36. NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes version 1.2015. National Comprehensive Cancer Network. 2014.

37. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010;115(3):453-74.

38. Metzeler KH, Becker H, Maharry K, Radmacher MD, Kohlschmidt J, Mrozek K, et al. ASXL1 mutations identify a high-risk subgroup of older patients with primary cytogenetically normal AML within the ELN Favorable genetic category. Blood 2011;118(26):6920-9.

39. Metzeler KH, Maharry K, Radmacher MD, Mrozek K, Margeson D, Becker H, et al. TET2 mutations improve the new European LeukemiaNet risk classification of acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 2011;29(10):1373-81.

40. Patel JP, Gonen M, Figueroa ME, Fernandez H, Sun Z, Racevskis J, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med 2012;366(12):1079-89.

41. Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med 2011;364(26):2496-506.

42. Papaemmanuil E, Cazzola M, Boultwood J, Malcovati L, Vyas P, Bowen D, et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. N Engl J Med 2011;365(15):1384-95.

43. Levis M. FLT3 mutations in acute myeloid leukemia: what is the best approach in 2013? Hematology Am Soc Hematol Educ Program 2013;2013:220-6.

44. Koszarska M, Bors A, Feczko A, Meggyesi N, Batai A, Csomor J, et al. Type and location of isocitrate dehydrogenase mutations influence clinical characteristics and disease outcome of acute myeloid leukemia. Leuk Lymphoma 2013;54(5):1028-35.

45. Bejar R, Stevenson KE, Caughey B, Lindsley RC, Mar BG, Stojanov P, et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol 2014;32(25):2691-8.

46. Itzykson R, Kosmider O, Cluzeau T, Mansat-De Mas V, Dreyfus F, Beyne-Rauzy O, et al. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. Leukemia 2011;25(7):1147-52.

47. Visconte V, Selleri C, Maciejewski JP, Tiu RV. Molecular pathogenesis of myelodysplastic syndromes. Transl Med UniSa 2014;8:19-30.

48. Ko M, Huang Y, Jankowska AM, Pape UJ, Tahiliani M, Bandukwala HS, et al. Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature 2010;468(7325):839-43.

49. Wei Y, Chen R, Dimicoli S, Bueso-Ramos C, Neuberg D, Pierce S, et al. Global H3K4me3 genome mapping reveals alterations of innate immunity signaling and overexpression of JMJD3 in human myelodysplastic syndrome CD34+ cells. Leukemia 2013;27(11):2177-86.

50. Itzykson R, Fenaux P. Epigenetics of myelodysplastic syndromes. Leukemia 2014;28(3):497-506.

51. Ivey A, Hills RK, Simpson MA, Jovanovic JV, Gilkes A, Grech A, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med 2016;374(5):422-33.

52. Buccisano F, Maurillo L, Del Principe MI, Del Poeta G, Sconocchia G, Lo-Coco F, et al. Prognostic and therapeutic implications of minimal residual disease detection in acute myeloid leukemia. Blood 2012;119(2):332-41.

53. Thol F, Kolking B, Damm F, Reinhardt K, Klusmann JH, Reinhardt D, et al. Next-generation sequencing for minimal residual disease monitoring in acute myeloid leukemia patients with FLT3-ITD or NPM1 mutations. Genes, Chromosomes & Cancer 2012;51(7):689-95.

54. Braun T, Carvalho G, Fabre C, Grosjean J, Fenaux P, Kroemer G. Targeting NF-kappaB in hematologic malignancies. Cell Death Differ 2006;13(5):748-58.

55. Du J, Huo J, Shi J, Yuan Z, Zhang C, Fu W, et al. Polymorphisms of nuclear factor-{kappa}B family genes are associated with development of multiple myeloma and treatment outcome in patients receiving bortezomib-based regimens. Haematologica 2011;96(5):729-37.

56. Coiffier B, Li W, Henitz ED, Karkera JD, Favis R, Gaffney D, et al. Prespecified Candidate Biomarkers Identify Follicular Lymphoma Patients Who Achieved Longer Progression-Free Survival with Bortezomib-Rituximab Versus Rituximab. Clin Cancer Res 2013;19(9):2551-61.

57. Ha TY. MicroRNAs in Human Diseases: From Cancer to Cardiovascular Disease. Immune Netw 2011;11(3):135-54.

58. Rhyasen GW, Starczynowski DT. Deregulation of microRNAs in myelodysplastic syndrome. Leukemia 2012;26(1):13-22.

59. Sokol L, Caceres G, Volinia S, Alder H, Nuovo GJ, Liu CG, et al. Identification of a risk dependent microRNA expression signature in myelodysplastic syndromes. Br J Haematol 2011;153(1):24-32.

60. Pardanani A, Finke C, Lasho TL, Al-Kali A, Begna KH, Hanson CA, et al. IPSS-independent prognostic value of plasma CXCL10, IL-7 and IL-6 levels in myelodysplastic syndromes. Leukemia 2012;26(4):693-9.

61. Chen WL, Wang JH, Zhao AH, Xu X, Wang YH, Chen TL, et al. A distinct glucose metabolism signature of acute myeloid leukemia with prognostic value. Blood 2014;124(10):1645-54.

62. Kornblith AB, Herndon JE, 2nd, Silverman LR, Demakos EP, Odchimar-Reissig R, Holland JF, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. J Clin Oncol 2002;20(10):2441-52.

63. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

64. Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer 2006;106(5):1090-8.

65. Oliva E, Nobile F, Dimitrov B. Development and validation of QOL-E© instrument for the assessment of health-related quality of life in myelodysplastic syndromes. Central European Journal of Medicine 2013;8(6):835-44.

66. Vidaza 25 mg/mL powder for suspension for injection [Summary of Product Characteristics]. Uxbridge, United Kingdom: Celgene Europe Ltd, 2014.

67. Von Hoff DD, Slavik M, Muggia FM. 5-Azacytidine. A new anticancer drug with effectiveness in acute myelogenous leukemia. Ann Intern Med 1976;85(2):237-45.

68. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.

69. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 2010;28(4):562-9.

70. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. Results of a phase 3, multicenter, randomized, open-label study of azacitidine (AZA) vs conventional care regimens (CCR) in older patients with newly diagnosed acute myeloid leukemia (AML). Haematologia (Budap) 2014;99(s1):788-89.

71. Schanz J, Tuchler H, Sole F, Mallo M, Luno E, Cervera J, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol 2012;30(8):820-9.

72. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;100(7):2292-302.

73. Silverman LR, McKenzie DR, Peterson BL, Holland JF, Backstrom JT, Beach CL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24(24):3895-903.

74. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.

75. 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.

76. Etienne A, Esterni B, Charbonnier A, Mozziconacci MJ, Arnoulet C, Coso D, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. Cancer 2007;109(7):1376-83.

15. APPENDICES

15.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

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

Source: Oken et al, 1982 [74].

15.2 Cockcroft-Gault Equation

For male patient/subject:

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

For female patient/subject:

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

15.3 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

15.4 Methods of Contraception Considered to be Effective

Acceptable 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 as highly effective. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
- oral
- intravaginal
- transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
- oral
- injectable
- implantable [2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence [4]

Methods that are Considered Less Highly Effective

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

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]

- cap, diaphragm or sponge with spermicide[5]

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

1) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
2) Contraception methods that in the context of this guidance are considered to have low user dependency.
3) 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.
4) 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.
5) 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.

15.5 New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac disease [75].

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

15.6 Excluded CYP3A Inducers

Use of strong CYP3A inducers listed in Table 15.a should be avoided during pevonedistat therapy.

Table 15.a In Vivo Inducers of CYP3A

Strong Inducers (≥80% decrease in AUC)
Carbamazepine
Phenytoin
Phenobarbital
Primidone
Rifabutin
Rifampin
Rifapentine
St. John's wort

Abbreviations: AUC=area under the plasma concentration-time curve.
Please refer to the following sources for additional information: medicine.iupui.edu/clinpharm/ddis/main-table/ and fda.gov/drugs/developmentapprovalprocess/developmentresources/%20druginteractionslabeling/ucm093664.htm.

15.7 Modified Charlson Comorbidity Index

Table 15.b Modified Charlson Comorbidity Index

Point	Comorbid Condition
1	Myocardial infarction
1	Congestive heart failure
1	Cerebrovascular disease
1	Ulcer
1	Hepatic disease (mild)
1	Diabetes (mild or moderate)
1	Pulmonary disease (moderate or severe)
1	Connective tissue disease
2	Diabetes (severe with end-organ damage)
2	Renal disease (moderate or severe)
2	Solid tumor (without metastases)
3	Hepatic disease (moderate or severe)
6	Solid tumor (with metastases)
	Total score

Source: From Etienne et al, 2007 [76].

15.8 Body Surface Area Calculation

Body surface area (BSA) should be calculated using a standard formula. An example formula follows:

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

OR

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

15.9 Formula for 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

15.10 Amendment 01 Rationale and Purposes

Rationale for Amendment 01

The original protocol received approval signatory on 25 February 2015. Based on the need to clarify information, modifications and/or revisions to the text were required. The study has not enrolled any patients.

The rationale for including low-marrow blast count (20%-30%) World Health Organization (WHO)-defined acute myelogenous leukemia (AML) is based on the fact that it had been previously classified as refractory anemia with excess blasts in transformation (RAEB-t), which was part of the myelodysplastic syndromes (MDS) spectrum, and that it is often treated with azacitidine-based therapy. In a phase 3 randomized trial, azacitidine significantly prolonged overall survival compared with conventional care regimens in patients with higher-risk MDS. In that trial, in a subgroup analysis of the 113 elderly patients previously classified as RAEB-t (now re-classified as low marrow blast AML), azacitidine significantly prolonged survival and was associated with fewer total days in the hospital than conventional care regimens.

The rationale for simplifying the schedule of events is based on the review of information presented in the last Development Safety Update Report (DSUR) (cumulative to 22 January 2015) where there was no change to the benefit-risk evaluation for pevonedistat. The sponsor also conducted preliminary analyses (data available as of 19 July 2015) of select safety parameters, including gamma glutamyl transpeptidase (GGT), urinalyses (including urobilinogen), and vital signs (including systolic blood pressure, diastolic blood pressure, and heart rate), and no safety concerns were identified.

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 females matches the contraception recommendation for males.

The rationale for removing the Quality of Life in Hematological Patients (myelodysplastic syndromes) (QOL-E) assessment at study centers outside the United States (US) is because validated translations of the questionnaire are not available for all countries in which the sponsor intends to enroll patients.

The definition of transformation to AML has been clarified to point out that peripheral blood samples can be used for patients for whom bone marrow examination is not possible. Specifications for sample handling have been added.

CCI [redacted]

Purposes for Amendment 01

The purposes of this amendment are to:

Study Population:

- Revise study population to include patients with low-blast AML.
- Revise the number of patients expected to be enrolled in the study.
- Clarify definition of progressive disease for patients with low-blast AML.
- Clarify timing of EFS visit for patients with HR MDS, CMML, or AML.

Study Objectives:

- Revise primary objective to reflect the addition of patients with low-blast AML.
- Revise secondary objectives to reflect the addition of patients with low-blast AML.
- CCI [redacted]
- Revise secondary objective to clarify that blood samples will be collected for determination of pevonedistat plasma concentration-time data to contribute to future population pharmacokinetic analyses of pevonedistat.

Study Endpoints:

- Revise primary endpoint to reflect the addition of patients with low-blast AML.
- Revise secondary endpoints to reflect the addition of patients with low-blast AML.
- Delete secondary endpoint regarding collection of pevonedistat plasma concentrations since this information is captured in a secondary objective.
- Add / revise secondary endpoints.
- Add / revise exploratory endpoints.

Inclusion/Exclusion Criteria:

- Revise inclusion criteria to allow for patients with low-blast AML.
- Revise inclusion criterion regarding direct bilirubin values for patients with Gilbert's syndrome.

- Update exclusion criteria to exclude patients with acute promyelocytic leukemia from enrolling in the study.
- Update exclusion criteria to exclude patients with prothrombin time (PT) or activated partial thromboplastin time (aPTT) > 1.5 upper limit of the normal range (ULN).

Study Drug Administration:

- Revise wording to emphasize that adherence to study drug dosing on specific days is strongly recommended. However, dosing may be delayed for safety reasons or unavoidable circumstances such as weather conditions affecting clinic accessibility.

Study Procedures:

- Revise study figure for patients with higher-risk myelodysplastic syndromes (HR MDS) and chronic myelomonocytic leukemia (CMML) (Diagram 1) and add a study figure for patients with low-blast AML (Diagram 2).
- Increase numbers of buccal swabs to be collected.
- Remove the QOL-E assessment for investigative centers outside the US.
- Revise language regarding the EORTC-QLQ-C30.
- Remove GGT from serum chemistry analytes from Cycle 2 and beyond.
- Remove urobilinogen from all urinalyses analytes from Cycle 2 and beyond.
- Update section on bone marrow aspirate and biopsy collection and analysis to reconcile language in the protocol.
- Revise language to emphasize that the investigator should make all efforts to obtain bone marrow samples for assessment of disease.
- Update section on bone marrow sample collection for disease assessment to indicate that cytogenetic assessments to determine Revised International Prognostic Scoring System (IPSS-R) will be performed for patients with higher-risk myelodysplastic syndromes (HR MDS) or chronic myelomonocytic leukemia (CMML). CCI [redacted]
- Revise section on prohibited concomitant medications.
- Revise language regarding administration of myeloid growth factors to indicate that the use of myeloid growth factors should be limited.
- Revise language on pregnancy testing to 1) remove the requirement for pregnancy testing at the EOT visit and 2) indicate that additional pregnancy testing may be required if requested by an institutional review board (IRB)/ independent ethics committee (IEC).
- Clarify that the Screening chest X-ray will not be done to confirm eligibility if it had been performed within 2 months before Screening.
- Add phosphate blood tests to Day 5 of each cycle (to be performed by a central laboratory).
- Revise timing of vital sign measurements to reflect that vital sign measurements will now be taken on select dosing days only instead of on all dosing days for both pevonedistat or azacitidine.

Statistical Methods:

- Update statistical methods section to revise hazard ratio calculations and confidence intervals along with the estimated number of event-free survival (EFS) events required.
- Add description of analyses for secondary efficacy endpoints.
- Revise section on timing of interim analyses (IA).

Administrative:

- Revise language regarding study duration.
- Delete text from the introduction that proposes karyotypes and molecular alterations, rather than blast counts, form the basis for the separation of MDS and AML since in this study, blast counts are being used to differentiate between HR MDS and low-blast AML.
- Update section on clinical data from the ongoing study with pevonedistat plus azacitidine.
- Update section on discontinuation of study drug treatment and patient replacement to indicate that patients with progressive disease may remain on study if they are deriving clinical benefit and that patients who do not receive study drug will not be replaced.
- Update section on reasons for withdrawal of patients from study.
- Add section on safety monitoring.
- Update section on study completion to indicate that a minimum of 6 cycles of treatment is strongly encouraged.
- Modify the period of contraception use after the last dose of study drug for women of childbearing potential to 4 months.
- Revise section on collection of hospitalization assessments.
- Revise section regarding the Independent Data Monitoring Committee (IDMC).
- Revise the section on packaging and labeling.
- Add the suspected unexpected serious adverse reactions (SUSARs) reporting section in order to expand the sponsor's responsibilities for reporting expected and unexpected adverse events (AEs).
- Update contact information for product complaints.
- Update the list of references.
- Update the protocol approval signatories.
- Structure text and clarify wording within the modified sections for improved clarity and readability.

Correct typographical errors, punctuation, grammar, and formatting.

15.11 Amendment 02 Rationale and Purposes

Rationale for Amendment 02

This protocol was revised to comply with requests received by regulatory agencies and the investigative sites. To mitigate reproductive and developmental hazards, additional pregnancy testing has been added at Day 1 of each Cycle and at end of treatment (EOT). Patients will also not be allowed to donate ova or sperm during the study and for 4 months following the last dose of study drug(s). In addition, examples of highly effective birth control methods have been included.

In this study, patients with higher-risk myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) may be allowed to continue study treatment if they meet the criteria for progressive disease (PD) based only on bone marrow blast count (without transformation to acute myelogenous leukemia [AML]) if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients with low-blast AML may also be allowed to continue study treatment even if they meet the criteria for PD based only on bone marrow blast counts if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients with PD who continue on study at the investigator's discretion should be reconsented before continuing study treatment.

The rationale to allow patients with therapy-related MDS, CMML, or low-blast AML associated with previous cytotoxic chemotherapy to be included in the study is based on the fact that patients with therapy-related MDS or AML have an equivalent outcome to certain patients with de novo disease. This is because cytogenetics has an important impact on the prognosis of patients with AML or MDS and is the strongest prognostic factor for overall survival. In patients with de novo MDS with similar adverse cytogenetics, survival is comparable to patients with therapy-related MDS.

Purposes for Amendment 02

The purposes of this amendment are to:

Clarify timing/consistency:

- Clarify the collection period for concomitant medications and procedures.

- Clarify the collection period for red blood cell and platelet transfusions (8 weeks before randomization through 30 days after the last dose of any study drug).
- Clarify the collection period for adverse events.
- Clarify that patients with low-blast AML at study entry will enter event-free survival follow-up when they have experienced PD.
- Add a window for the Cycle 1 Day 15 visit (±1 day).
- Add a window for the Cycle 1 Day 21 visit (±1 day).
- Clarify the window for screening assessments (within 28 days before randomization).
- Clarify the collection time for the Cycle 2 Day 22 bone marrow aspirate sample for molecular analysis.
- Change the minimum time between pevonedistat dosing from 48 hours to 1 full calendar day.
- Clarify the collection time for the bone marrow aspiration for blast count (eligibility) versus for molecular analysis.
- Add a window for pevonedistat administration (60±10 minutes).

Clinical Experience:

- Clarify that final data for Study C15009 are not yet available.
- Clarify pevonedistat nonclinical pharmacokinetics and risk assessment for drug-drug interactions.

Rationale:

- Provide the rationale for the azacitidine dosing schedule.
- Provide the rationale for including minimal residual disease assessment as a measurement of depth of response.
- Clarify the rationale for using the EORTC-QLQ-30 and QOL-E as health-related quality of life (HRQOL) instruments.

Objectives/Endpoints:

- Clarify that relapse includes relapse from complete remission (CR) and partial remission (PR) for patients with MDS/CMML, and relapse from CR for patients with AML.
- CCI
- [redacted]

Inclusion/Exclusion Criteria:

- Specify that clinical laboratory values used for eligibility will need to be repeated if performed more than 3 days before the first dose of study drug.
- Allow patients with therapy-related MDS, CMML, or low-blast AML associated with previous cytotoxic chemotherapy (eg, alkylating agents, topoisomerase inhibitors) to be included in the study.

- Include lenalidomide as an example of an excluded antileukemic/anti-MDS drug.
- Specify that treatment with other antileukemic/anti-MDS drugs is not allowed within 14 days before the first dose of any study drug.
- Provide definition of postmenopausal.
- Specify highly effective contraception methods.
- Specify that patients who have received systemic antineoplastic therapy or radiotherapy for other malignant conditions within 12 months before the first dose of any study drug, except for hydroxyurea, will be excluded from the study.
- Specify that donation of ova is excluded during the study and for 4 months after the last dose of study drug(s).
- Specify that donation of sperm is excluded during the study and for 4 months after the last dose of study drug(s).

Study Procedures:

- Specify that additional electrocardiograms may be performed as clinically indicated.
- Specify that clinical laboratory evaluations used for eligibility should be performed by a central laboratory.
- Add pregnancy tests at Day 1 of each cycle and at EOT.
- Specify that HRQOL questionnaires will be paper-based.
- Clarify that patients should complete the patient-reported outcome questionnaires on their own.
- Specify that translation and validation of the QOL-E is now available outside of the United States.
- Clarify the description of the EQ-5D-5L.
- Add transfusion data collection to hospitalization assessments.
- Specify that acceptable bone marrow biopsy samples will include 5 unstained slides (charged slides) from core biopsy samples.
- Clarify that hematologic improvement is relevant to MDS/CMML but *not* AML.
- Specify that patients with PD based only on bone marrow blast counts who continue on study at the investigator discretion must be reconsented before continuing study treatment.
- Clarify that mutation analysis is not required if it is not performed routinely per country/institutional guidelines.
- Specify that the PD response criterion for altering the natural history of MDS and CMML includes new transfusion dependence.
- Add relapse after CR as a response criterion for AML.
- [redacted] CCI
- Add bone marrow aspirate for molecular analysis at the end of Cycle 4 and at the end of Cycle 7 (for patients who do not have a confirmed CR at Cycle 4).

Pevonedistat Labeling and Storage:

- Update the Pevonedistat product description and labeling.

- Update the storage/stability requirements for Pevonedistat/IV preparation to be consistent with directions for use in the Pharmacy Manual.
- Remove the vial size specified for Pevonedistat Concentrate for Solution for Infusion.

Administrative:

- Specify that current information on azacitidine may also be found in the European Union Summary of Product Characteristics.
- Correct the serum electrolyte toxicity grade needed to permit continued administration of azacitidine.
- Specify that transfusions will be collected on an electronic case report form (eCRF), not on a concomitant medication eCRF.
- Update contact information for product complaints.
- Update the list of references.
- Correct typographical errors, punctuation, grammar, and formatting.

15.12 Amendment 03 Rationale and Purposes

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 employ a definition of event-free survival (EFS) that is consistent with the global registration Study Pevonedistat-3001 and provide a more clearly defined clinical endpoint for patients with low-blast acute myelogenous leukemia (AML). This change will facilitate integration of this supportive study with the global registration study results. This change in EFS definition affects the primary objective and primary endpoint of the study. For patients with low-blast AML, progressive disease or relapse after complete remission (CR) has been removed from the definition of an *event* and an *event* in patients with low-blast AML is now defined only as *death*.

Changes in Amendment 03

1. Realign the analysis of the primary objective and endpoint as related to the change in the definition of an *event* for patients with low-blast AML.
2. Specify the change in the follow-up process for patients with low-blast AML.
3. Specify the trigger initiating the timing of the overall survival final analysis and other factor(s) that might affect the duration of the study.
4. Specify the changes used for determination of sample size.
5. Specify the timing of the second interim analysis to a specific number of events.
6. Clarify that Kaplan-Meier estimates and CIs of 6-month and 1-year survival rates will be provided based on the intent-to-treat population.
7. Append "relapse from CR" to Study Overview Diagram 2 for patients with AML.
8. Update the investigator responsibilities for compliance with updated International Council for Harmonisation guidelines.

15.13 Amendment 04 Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment 04 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Update the pharmacokinetic profile of pevonedistat and risk assessment for drug-drug interactions.

The primary change occurs in Section 1.4.1 Nonclinical Pharmacokinetics and Risk Assessment for Drug-Drug Interactions

Initial wording:	In vitro pevonedistat is metabolized via hydroxylation and oxidation, predominantly by CYP3A4 with a small contribution from CYP2D6. Preliminary PK evaluations from 26 patients with advanced solid tumors in an ongoing open-label drug-drug interaction (DDI) study (Study C15011) showed that steady-state fluconazole (classified as a moderate CYP3A inhibitor) appeared to have minimal effect (13% increased area under the plasma concentration versus time curve from zero to infinity [AUC_{inf}] on average) on the single IV PK of pevonedistat, while systemic exposure of pevonedistat appeared to increase by 23% on average in the presence of itraconazole (classified as a strong CYP3A [and P-gp] inhibitor). On the basis of these findings, administration of pevonedistat with strong CYP3A inhibitors or inducers should be avoided.
Amended or new wording:	In vitro pevonedistat is metabolized via hydroxylation and oxidation, predominantly by CYP3A4 with a small contribution from CYP2D6. ~~Preliminary PK evaluations from 26 patients with advanced solid tumors in an ongoing open-label~~ **Results from the completed** drug-drug interaction (DDI) ~~study~~ ~~(~~Study C15011~~)~~ ~~showed~~ **indicated** that ~~steady-state~~ **multiple-dose administration of** fluconazole**,** ~~(classified as~~ a moderate CYP3A inhibitor**,** ~~appeared to have minimal effect (13% increased area under the plasma concentration versus time curve from zero to infinity [AUC_{inf}] on average) on the single IV~~ **had no clinically relevant effects on the** PK of pevonedistat.~~, while~~ **Pevonedistat** systemic exposure ~~of pevonedistat appeared to increase by 23% on average~~ in the presence of itraconazole**,** ~~(classified as~~ a strong CYP3A ~~[and P-gp]~~ inhibitor~~)~~, ~~On the basis of these findings, administration of pevonedistat with strong CYP3A inhibitors or inducers should be avoided.~~ **was only minimally increased compared with that in the absence of itraconazole (geometric mean dose-normalized AUC_{∞} ratio of 1.14 [90% CI, 1.07 to 1.23]). The 14% increase in the pevonedistat geometric mean dose-normalized AUC was not considered clinically meaningful when viewed in the context of pevonedistat overall PK variability (coefficient of variation in AUC_{∞}, 16%-34%), supporting inference of the lack of a clinically relevant**

	effect of itraconazole, a strong CYP3A inhibitor on total systemic exposure (AUC) of pevonedistat (see Section 1.6.3).
Rationale for Change: Update pevonedistat PK to reflect most current information on DDIs.	
Section 1.6.3 Potential for Drug-Drug Interactions also contains this change.	
Change 2: Update the primary objective and endpoint of the study to OS.	
Primary changes occur in Section 2.1 Primary Objective and Section 3.1 Primary Endpoint.	
Initial wording:	**2.1 Primary Objective** The primary objective is: • To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves event-free survival (EFS) when compared to single-agent azacitidine; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death (see Section 7.4.21). **3.1 Primary Endpoint** The primary endpoint is: • EFS; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death (see Section 7.4.21).
Amended or new wording:	**2.1 Primary Objective** The primary objective is: • To determine in patients with HR MDS~~, CMML,~~ **or CMML** and low-blast AML whether the combination of pevonedistat and azacitidine improves ~~event-free survival (EFS)~~ **overall survival (OS)** when compared ~~to~~**with** single-agent azacitidine~~; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death (see Section 7.4.21)~~. **3.1 Primary Endpoint** The primary endpoint is: • ~~EFS; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death (see Section 7.4.21).~~

- **OS**

Rationale for Change: OS is a clearly defined endpoint that is commonly used in studies with patients who have HR MDS, CMML, or low-blast AML.

The Protocol Summary also contains the change in the primary objective.

Change 3: Update secondary objectives and endpoints of the study, including addition of EFS, and clarify definitions of response to the study treatment in the secondary endpoints.

Primary changes occur in Section 2.2 Secondary Objectives and Section 3.2 Secondary Endpoints.

Initial wording:

2.2 Secondary Objectives

The secondary objectives are:

- To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves overall survival (OS) when compared to single-agent azacitidine.
- To determine in patients with HR MDS, CMML and low-blast AML whether the combination of pevonedistat and azacitidine improves 6-month and 1-year survival rates when compared to single-agent azacitidine.
- To determine in patients with HR MDS and CMML whether the combination of pevonedistat and azacitidine delays time to AML transformation when compared to single-agent azacitidine.
- To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine, when compared to single agent azacitidine, improves the rate of: CR, CR plus partial remission (CR+PR), and/or overall response. Overall response in HR MDS and CMML is defined as CR+PR+hematologic improvement [HI]); overall response in low-blast AML is defined as CR+PR.
- To determine in patients with HR MDS, CMML and low-blast AML whether the combination of pevonedistat and azacitidine, when compared to single agent azacitidine, improves the rate of CR, CR+PR, as well as the ORR by Cycle 4.
- To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine, when compared to single-agent azacitidine, improves duration of CR, CR+PR, and/or overall response.
- To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves time to first CR or PR when compared to single-agent azacitidine.
- To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine delays time to subsequent therapy when compared to single-agent azacitidine.

Subsequent therapy is defined as agent(s) with antileukemic/anti-MDS activity (eg, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.

- To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves rate of transfusion independence when compared to single-agent azacitidine. RBC or platelet transfusion independence requires that the patient receive no RBC or platelet transfusions, respectively, for a period of at least 8 weeks.
- To determine in patients with HR MDS, CMML and low-blast AML whether the combination of pevonedistat and azacitidine reduces the percent of patients who have at least one inpatient hospital admission(s) related to HR MDS, CMML, or low-blast AML when compared to single-agent azacitidine.
- To determine in patients with HR MDS, CMML and low-blast AML whether the combination of pevonedistat and azacitidine delays time to PD, relapse, or death when compared to single-agent azacitidine.
- To evaluate in patients with HR MDS, CMML and low-blast AML, the safety of the combination of pevonedistat and azacitidine when compared to single-agent azacitidine.
- To collect in patients with HR MDS, CMML, and low-blast AML, plasma concentration-time data for pevonedistat to contribute to future population PK analyses of pevonedistat.

3.2 Secondary Endpoints

The secondary endpoints are:

- OS.
- Time to AML transformation in HR MDS and CMML patients.
- CR, CR+PR, overall response (CR+PR+HI for HR MDS and CMML; CR+PR for low-blast AML).
- CR, CR+PR, overall response (CR+PR+HI for HR MDS and CMML; CR+PR for low-blast AML) by Cycle 4.
- Duration of CR, duration of CR+PR, duration of overall response (CR+PR+HI for HR MDS and CMML; CR+PR for low-blast AML).
- Time to first CR or PR.

Amended or new wording:

2.2 Secondary Objectives

The secondary objectives are:

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

- **To determine in patients with HR MDS or CMML and low-blast AML whether the combination of pevonedistat and azacitidine improves event-free survival (EFS) when compared with single-agent azacitidine; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death (see Section 7.4.21).**
- To determine in patients with HR MDS~~,~~ **or** CMML and low-blast AML whether the combination of pevonedistat and azacitidine improves 6-month and 1-year survival rates when compared ~~to~~**with** single-agent azacitidine.
- To determine in patients with HR MDS ~~and~~ **or** CMML whether the combination of pevonedistat and azacitidine delays time to AML transformation when compared ~~to~~**with** single-agent azacitidine.
- To determine in patients with HR MDS~~,~~ **or** CMML~~,~~ and low-blast AML whether the combination of pevonedistat and azacitidine, when compared ~~to~~**with** single-agent azacitidine, improves the rate of~~:~~ ~~CR~~, **complete remission (CR) (composite CR [CR + Cri] in patients with low-blast AML)**, CR plus partial remission (**composite** CR + PR **for patients with low-blast AML),** overall response**, and/or CR (not including CRi) in low-blast AML**. Overall response in HR MDS ~~and~~ **or** CMML is defined as CR + PR + hematologic improvement (~~[~~HI~~]~~); overall response in low-blast AML is defined as CR + **CRi** + PR.
- To determine in patients with HR MDS~~,~~ **or** CMML and low-blast AML whether the combination of pevonedistat and azacitidine, when compared ~~to~~**with** single-agent azacitidine, improves the rate of CR~~,~~ ~~CR+PR, as well as he ORR~~ **(composite CR [CR + Cri] in patients with low-blast AML), CR + PR (composite CR + PR in patients with low-blast AML), the overall response rate (ORR), as well as CR (not including Cri) in low-blast AML** by Cycle 4.
- To determine in patients with HR MDS~~,~~ **or** CMML~~,~~ and low-blast AML whether the combination of pevonedistat and azacitidine, when compared ~~to~~**with** single-agent azacitidine, improves duration of CR~~,CR+PR,and/or~~ **(composite CR [CR + CRi] in patients with low-blast AML), CR + PR (composite CR + PR in patients with low-blast AML),** overall response**, and/or CR (not including Cri) in patients with low-blast AML**.
- To determine in patients with HR MDS~~,~~ **or** CMML~~,~~ and low-blast AML whether the combination of pevonedistat and azacitidine improves time to first CR **(CR for HR MDS/CMML and low-blast AML; CR + CRi [composite CR] for low-blast AML),** or PR when compared **with** single-agent azacitidine.
- To determine in patients with HR MDS~~,~~ **or** CMML~~,~~ and low-blast AML whether the combination of pevonedistat and azacitidine delays time to subsequent therapy when compared ~~to~~**with** single-agent azacitidine. Subsequent therapy is defined as agent(s) with

antileukemic/anti-MDS activity (eg, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.

- To determine in patients with HR MDS~~,~~ **or** CMML~~,~~ and low-blast AML whether the combination of pevonedistat and azacitidine improves rate of transfusion independence when compared ~~to~~**with** single-agent azacitidine. RBC or platelet transfusion independence requires that the patient receive no RBC or platelet transfusions, respectively, for a period of at least 8 weeks.
- To determine in patients with HR MDS~~,~~ **or** CMML and low-blast AML whether the combination of pevonedistat and azacitidine reduces the percent of patients who have at least one inpatient hospital admission(s) related to HR MDS~~,~~ **or** CMML, or low-blast AML when compared ~~to~~**with** single-agent azacitidine.
- To determine in patients with HR MDS~~,~~ **or** CMML and low-blast AML whether the combination of pevonedistat and azacitidine delays time to PD, relapse, or death when compared ~~to~~**with** single-agent azacitidine.
- To evaluate in patients with HR MDS~~,~~ **or** CMML and low-blast AML~~,~~ the safety of the combination of pevonedistat and azacitidine when compared ~~to~~**with** single-agent azacitidine.
- To collect in patients with HR MDS~~,~~ **or** CMML~~,~~ and low-blast AML~~,~~ plasma concentration-time data for pevonedistat to contribute to future population PK analyses of pevonedistat.

3.2 Secondary Endpoints

The secondary endpoints are:

- ~~OS.~~
- **EFS; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death (see Section 7.4.21).**
- Time to AML transformation in **patients with** HR MDS **or** ~~and~~ CMML ~~patients~~.
- CR, ~~CR+~~ **(CR for HR MDS and CMML; CR + CRi [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) +** PR, overall response (CR+PR+HI for HR MDS and CMML; CR+ **CRi +** PR for low-blast AML)**, CR (not including CRi) in low-blast AML**.
- CR~~, CR+~~ **(CR for HR MDS and CMML; CR + CRi [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) +** PR, overall response (CR + PR + HI

for HR MDS and CMML; CR~~+~~ **+ CRi +** PR for low-blast AML) **by Cycle 4, CR (not including CRi) in low-blast AML** by Cycle 4.

- Duration of CR~~, duration of CR+~~ **(CR for HR MDS and CMML, CR + Cri [composite CR] for low-blast AML), CR (CR for HR MDS and CMML; CR + CRi for low-blast AML) +** PR, ~~duration of~~ overall response (CR + PR + HI for HR MDS and CMML; CR + **CRi +** PR for low-blast AML)**, and duration of CR (not including CRi) in low-blast AML.**
- Time to first CR ~~or PR~~ **(CR for HR MDS/CMML and low-blast AML; CR + CRi [composite CR] for low-blast AML) or PR for HR MDS/CMML and low-blast AML**.

Rationale for Change: Update secondary objectives and endpoints to include EFS and clarify definitions of response.

The Protocol Summary also contains the changes in the secondary objectives.

Change 4: Update exploratory objectives and endpoints. CCI [redacted]

Primary changes occur in Section 2.3 Exploratory Objectives and Section 3.3 Exploratory Endpoints

Initial wording:

2.3 Exploratory Objectives

The exploratory objectives include:

CCI [redacted]

CCI

[redacted]

Amended or new wording:

2.3 Exploratory Objectives

The exploratory objectives include:

CCI

[redacted]

CCI [redacted]

Rationale for Change: Update exploratory objectives and endpoints, also CCI [redacted]

The Protocol Summary also contains the changes to exploratory objectives.

Change 5: Update the percentage of patients with OS events initiating the timing of the OS analysis and duration of the study.

Primary change Section 4.3 Duration of Study

Initial wording:	Patients, including those who achieve a CR, may receive study treatment until they experience PD or discontinuation for any other reason outlined in Section 7.5. Patients will be followed until approximately 60 OS events have occurred or 24 months after the enrollment of the last patient, whichever occurs first, or termination of the study by the sponsor.
Amended or new wording:	Patients, including those who achieve a CR, may receive study treatment until they experience PD or discontinuation for any other reason outlined in Section 7.5. Patients will be followed until approximately 60**% of patients with HR MDS/CMML have experienced** OS events ~~have occurred or 24 months after the enrollment of the last patient, whichever occurs first~~, or termination of the study by the sponsor. **Patients who are still receiving study treatment and continuing to derive clinical benefit may continue to receive pevonedistat at the discretion of the sponsor; the continuation of treatment may occur in a manner other than under the study protocol, in accordance with local regulations.**

Rationale for Change: To provide sufficiently mature OS data at the time of final analysis.

The Protocol Summary also contains this change.

Change 6: Update table for concomitant medications that are excluded while receiving single-agent azacitidine study treatment.

Primary change occurs in Section 6.4 Excluded Concomitant Medications and Procedures

Initial wording:	**Table 6.a Concomitant Medications Excluded During the Study: Single-Agent Azacitidine Arm** **Therapy** Any investigational agent including agents commercially available for indications other than MDS, CMML, or low-blast AML, including but not limited to androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]
Amended or new wording:	**Table 6.a Concomitant Medications Excluded ~~During the~~ While Receiving Study Treatment: Single-Agent Azacitidine Arm** **Therapy** Any investigational agent ~~including agents~~ **for MDS, CMML, or low-blast AML, or** commercially available ~~for indications other than~~ **agents used in** MDS, CMML, or low-blast AML, including ~~but not limited to~~ androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]

Rationale for Change: Clarify the exclusion of investigational or commercially available agents used to treat patients with HR MDS/CMML or low-blast AML while patients are receiving study treatment.

Change 7: Update table for concomitant medications that are excluded while receiving combination treatment pevonedistat + azacitidine.

Primary change occurs in Section 6.4 Excluded Concomitant Medications and Procedures, Table 6.b Concomitant Medications Excluded While Receiving Study Treatment: Combination Pevonedistat Plus Azacitidine Arm

Initial wording:

Table 6.b Concomitant Medications Excluded During the Study: Combination Pevonedistat Plus Azacitidine Arm

Therapy	Comment/Exceptions
Strong CYP3A inhibitors or inducers (see Section 15.6)	Excluded, but limited use of the azole antifungal agent, voriconazole, is permitted only if clinically necessary and no suitable alternative exists. The patient may receive voriconazole 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), Friday (Day 5) schedule, then voriconazole 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.
Any investigational agent other than pevonedistat, including agents commercially available for indications other than MDS, CMML, or low-blast AML including but not limited to androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]	

Amended or new wording:

Table 6.b Concomitant Medications Excluded ~~During the~~ While Receiving Study Treatment: Combination Pevonedistat Plus Azacitidine Arm

Therapy	Comment/Exceptions
Strong CYP3A ~~inhibitors or~~ inducers (see Section 15.6)	~~Excluded, but limited use of the azole antifungal agent, voriconazole, is permitted only if clinically necessary and no suitable alternative exists. The patient may receive voriconazole 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), Friday (Day 5) schedule, then voriconazole 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.~~
	Any investigational agent other than pevonedistat, ~~including agents~~ **for MDS, CMML, or low-blast AML, or** commercially available ~~for indications other than~~ **agents used in** MDS, CMML, or low-blast AML**,** including ~~but not limited to~~ androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]	

Rationale for Change: Include in the table only strong CYP3A inducers that may reduce pevonedistat exposures (remove restriction on CYP3A inhibitors on the basis of results of recent studies)

Change 8: Add section for posttrial access to study medication.

Primary change occurs in Section 7.11 Posttrial Access

Added text:

7.11 Post-Trial Access

7.11.1 Post-Trial Access

If an open-label, rollover, posttrial access (PTA) study should become an option and the investigator and the sponsor agree that a patient would derive benefit from continued treatment or would be harmed without continued access to the medication, the patient may be given the opportunity to enroll. The patient would then be able to continue receive pevonedistat (if randomized to the combination arm).

7.11.2 Duration of PTA

In the event of a rollover PTA study, continued access to pevonedistat for participants will be terminated for those individuals

	who no longer benefit from treatment (eg, their disease has progressed or treatment is no longer tolerable), the benefit-risk no longer favors the individual, an appropriate alternative therapy becomes available, or pevonedistat becomes available either commercially or via another access mechanism. PTA may be terminated in a country or geographical region where the development of pevonedistat has been suspended or stopped by the sponsor, or pevonedistat can no longer be supplied.

Rationale for Change: Text added for information on program-level PTA for pevonedistat.

Change 9: Specify changes for determination of sample size to align with new primary endpoint.

Primary change occurs in Section 8.1.1 Determination of Sample Size

Initial wording:	Assuming an exponential distribution for EFS, a total of approximately 60 EFS events will be required to detect a hazard ratio of 0.585 (median EFS of 22.2 months in the Combination Pevonedistat Plus Azacitidine Arm versus 13 months in the Single-Agent Azacitidine Arm) with approximately 85% power using a 1-sided log-rank test at a 15% overall significance level. Approximately 117 patients will be randomized in a 1:1 ratio to receive either the combination of pevonedistat and azacitidine or single-agent azacitidine, assuming an enrollment rate that increases from an initial 1 patient per month to 12 patients per month after 7 months. Sixty EFS events are estimated to occur within approximately 28 months from the enrollment of the first patient. This estimated period includes a 14-month accrual period and an additional 14-month follow-up from the last patient enrolled. EFS assumptions for single-agent azacitidine are based on a phase 3 study of azacitidine in MDS(https://clinicaltrials.gov/ct2/show/NCT00071799?term=azacitidine+MDS&no_unk=Y&rank=32, accessed 13 February 2015).
Amended or new wording:	~~Assuming an exponential distribution for EFS, a total of approximately 60 EFS events will be required to detect a hazard ratio of 0.585 (median EFS of 22.2 months in the Combination Pevonedistat Plus Azacitidine Arm versus 13 months in the Single-Agent Azacitidine Arm) with approximately 85% power using a 1-sided log-rank test at a 15% overall significance level.~~ Approximately 117 patients will be randomized in a 1:1 ratio to receive either the combination of pevonedistat and azacitidine or single-agent azacitidine~~, assuming an enrollment rate that increases from an initial 1 patient per month to 12 patients per month after 7 months~~. ~~Sixty EFS events are estimated to occur within approximately 28 months from the enrollment of the first patient. This estimated period~~

	~~includes a 14 month accrual period and an additional 14-month follow-up from the last patient enrolled~~. ~~EFS assumptions for single-agent azacitidine are based on a phase 3 study of azacitidine in MDS(https://clinicaltrials.gov/ct2/show/NCT00071799?term=azacitidine+MDS&no_unk=Y&rank=32, accessed 13 February 2015).~~

Rationale for Change: Remove the previous specification of EFS event size because EFS is no longer the primary endpoint.

Change 10: Clarify definition of safety population for purposes of analysis.

Primary change occurs in Section 8.1.3 Populations for Analysis

Initial wording:	• Safety population: The safety population is defined as all patients who receive at least 1 dose of pevonedistat plus azacitidine or azacitidine alone. Patients will be analyzed according to the actual treatment they received. Patients who received any dose of study drug (pevonedistat or azacitidine) will be included in the Combination Pevonedistat Plus Azacitidine Arm, and patients who did not receive any dose of pevonedistat will be included in the Single-Agent Azacitidine Arm, regardless of their randomized treatment.
Amended or new wording:	• Safety population: The safety population is defined as all patients who receive at least 1 dose of pevonedistat plus azacitidine or azacitidine alone. Patients will be analyzed according to the actual treatment they received. Patients who received any dose of ~~study drug~~ (pevonedistat ~~or azacitidine)~~ will be included in the Combination Pevonedistat Plus Azacitidine Arm, and patients who did not receive any dose of pevonedistat**, but received at least 1 dose of azacitidine,** will be included in the Single-Agent Azacitidine Arm, regardless of their randomized treatment.

Rationale for Change: Change made for clarification.

Change 11: Specify changes in general methodology for analysis of efficacy.

Primary change occurs in Section 8.1.6.1 General Methodology

Initial wording:	The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable) will also be provided, along with their 2-sided 70% CIs and 2-sided 95% CIs for time to event data. P values from statistical tests will be based on 2-sided tests with a 30% significance level, which is equivalent to 1 sided tests with a 15% significance level.
Amended or new wording:	The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable) will also be provided, along with their 2-sided ~~70% CIs and 2-~~

~~sided~~ 95% CIs for time to event data. ~~P values from statistical tests will be based on 2-sided tests with a 30% significance level, which is equivalent to 1-sided tests with a 15% significance level.~~

Rationale for Change: To align the general methodology for analysis of efficacy with the removal of EFS as the primary endpoint.

Change 12: Specify analyses of primary efficacy endpoint OS.

Primary change occurs in Section 8.1.6.2 Analyses of Primary Efficacy Endpoints

Initial wording:	The analysis of the primary efficacy endpoint, EFS, will be based on the ITT population. For patients with HR MDS/CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death. EFS is defined as the time from randomization to the occurrence of an event. Stratified log-rank test will be used to compare EFS between the 2 arms (see Section 8.1.2 for stratification factors). The hazard ratios along with the 2-sided 70% CIs and 95% CIs will be estimated using the unadjusted stratified Cox model. The proportional hazard assumptions will be examined and sensitivity analysis will be conducted if appropriate. The Kaplan-Meier survival curves and Kaplan Meier medians (if estimable), along with the 70% and 95% CIs, will also be provided for each treatment group.
Amended or new wording:	The analysis of the primary efficacy endpoint, **OS** ~~EFS~~, will be based on **HR MDS/CMML patients and** the ITT population **separately**. ~~For~~ **OS will be analyzed when approximately 60% of** patients with HR MDS/CMML~~, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death. EFS is defined as the time from randomization to the occurrence of an event. Stratified~~ **have experienced OS events, or termination of the study by the sponsor.** **OS will be calculated from date of randomization to the date of patient death due to any cause. Patients without documented death at the time of the analysis will be censored at the date that the patient was last known to be alive. Unstratified** log-rank test will be used to compare **OS** ~~EFS~~ between the 2 **treatment** arms ~~(see Section 8.1.2 for stratification factors). The hazard~~ **Hazard** ratios**,** along with the 2-sided ~~70% CIs and~~ 95% CIs**,** will be estimated using the unadjusted**,** ~~stratified~~ **unstratified** Cox model. The proportional hazard assumptions will be examined and sensitivity analysis will be conducted if appropriate. ~~The~~ Kaplan-Meier ~~survival~~ curves and Kaplan-Meier medians (if estimable), ~~along~~ **together** with the ~~70% and~~ 95% CIs, will ~~also~~ be ~~provided~~ **calculated** for each treatment group.

Rationale for Change: To align with OS as the primary endpoint.

Change 13: Clarify methodology for analysis of secondary efficacy endpoints, including those that are response-related.

Primary change occurs in Section 8.1.6.3 Analyses of Secondary Efficacy Endpoints

Initial wording:

If the secondary efficacy endpoint is response related, such as CR or duration of CR, the response-evaluable population will be used. Otherwise the analysis will be based on the ITT population.

For low-blast AML patients, all CR includes both complete remission (CR) and complete remission with incomplete count recovery (CRi).

Overall Survival

OS will be calculated from date of randomization to the date of patient death due to any cause. Patients without documented death at the time of the analysis will be censored at the date that the patient was last known to be alive. Stratified log-rank test will be used to compare OS between the 2 treatment arms. Hazard ratios, along with the 2-sided 70% and 95% CIs will be estimated using the unadjusted stratified Cox model. The proportional hazard assumptions will be examined and sensitivity analysis will be conducted if appropriate. Kaplan-Meier curves and Kaplan-Meier medians (if estimable), together with the 70% and 95% CIs, will be calculated for each treatment group.

Six-Month and One-Year Survival Rate

Kaplan-Meier estimates and the 70% and 95% CIs of 6-month and 1-year survival rates will be provided based on the ITT population.

Time to AML Transformation

Time to AML transformation is defined as time from randomization to documented AML transformation. This definition only applies to HR MDS and CMML patients, so this analysis will only be carried out in this subgroup. Patients who died before progression to AML will be censored. Stratified log-rank test will be used to compare time to AML transformation between the 2 arms. Hazard ratio and its 2-sided 70% and 95% CI will be calculated using the stratified Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the 70% and 95% CIs, will be calculated for each treatment group.

CR/CR+PR/Overall Response (CR+PR+HI)

CR/CR+PR/overall response calculations will be based on the response-evaluable population.

The number and percentage of patients who achieved CR/CR+PR/overall response (CR+PR+HI for patients with HR MDS/CMML, CR+PR for

patients with low-blast AML), respectively, will be summarized by treatment group. CR rate/CR+PR rate/overall response rate, respectively, will be tested using the stratified Cochran-Mantel-Haenszel (CMH) chi square test. The CMH chi-square test p-value, the relative risk with its 2-sided 70% and 95% CI will be calculated. The absolute rate difference will be provided with its 70% and 95% CI.

CR/CR+PR/Overall Response (CR+PR+HI) by Cycle 4

The number and percentage of patients who achieved CR/CR+PR/overall response (CR+PR+HI for patients with HR MDS/CMML, CR+PR for patients with low-blast AML) by Cycle 4, respectively, will be summarized by treatment group. CR rate/CR+PR rate/overall response rate by Cycle 4, respectively, will be tested using the stratified Cochran-Mantel-Haenszel (CMH) chi-square test. The CMH chi-square test p-value, the relative risk with its 2-sided 70% and 95% CI will be calculated. The absolute rate difference will be provided with its 70% and 95% CI.

Duration of CR/CR+PR/Overall Response (CR+PR+HI)

Calculations of duration of responses will be based on the response-evaluable population.

Duration of CR/CR+PR/overall response (CR+PR+HI for patients with HR MDS/CMML, CR+PR for patients with low-blast AML), respectively, will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates.

Time to First CR or PR

Analysis of time to first CR or PR will be based on the response-evaluable population.

Time to first CR or PR is defined as time from randomization to first documented CR or PR, whichever occurs first. Stratified log-rank test will be used to compare time to first CR or PR between the 2 arms. Hazard ratio and its 2-sided 70% and 95% CI will be calculated using the stratified Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the 70% and 95% CIs, will be calculated for each treatment group.

Time to Subsequent Therapy

Analysis of time to subsequent therapy will be based on the ITT population.

Stratified log-rank test will be used to compare time to subsequent therapy between the 2 arms. Hazard ratio and its 2-sided 70% and 95% CIs will be calculated using stratified Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the 70%

	and 95% CIs will be calculated for reach treatment group. **Rate of Transfusion Independence** Analysis of RBCs and platelet-transfusion independence will be based on the ITT population. A patient is defined as RBC or platelet-transfusion independent if he/she receives no RBC or platelet transfusions for a period of at least 8 weeks [13,73]. Rate of transfusion independence is defined as number of patients who become transfusion independent divided by the number of patients who are transfusion dependent at Baseline. The number of patients who are transfusion dependent/independent at Baseline and post Baseline, as well as rate of transfusion independence, will be summarized by treatment group. Rate of transfusion independence will be tested using stratified CMH test. P values and 2-sided 70% and 95% CIs of the relative risk will be provided. **Percent of Inpatient Hospitalizations Related to HR MDS, CMML, or AML** Analysis of number of inpatient hospital admissions related to HR MDS, CMML, or AML will be based on the ITT population. Inpatient hospital admission data will be collected through transformation to AML (HR MDS/CMML patients) or disease progression (low-blast AML patients) or until initiation of subsequent therapy (all patients), whichever occurs first. The number and percentage of patients who have any hospitalizations related to HR MDS, CMML, or AML will be summarized by treatment group. The absolute rate difference will be provided with its 70% and 95% CI.
	Time to PD, Relapse, or Death Analysis of time to PD, relapse, or death will be based on the ITT population. Time to PD, relapse, or death is defined as the time from randomization until disease progression, or relapse, or death due to any cause, whichever occurs first. Stratified log-rank test will be used for comparison between the 2 arms. The hazard ratios along with the 2 sided 70% and 95% CIs will be estimated using the unadjusted stratified Cox model. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), along with the 70% and 95% CIs, will also be provided for each treatment group.
Amended or new wording:	If the secondary efficacy endpoint is response related, such as ~~CR or duration of~~ CR, the response-evaluable population ~~will be used. Otherwise~~ **of patients with HR MDS/CMML, patients with low-blast AML, and the overall patient population will be used separately, if**

appropriate. Duration of the response-related endpoint will be analyzed based on the corresponding responders; otherwise, the analysis will be based on **HR MDS/CMML patients and** the ITT population **separately**.

For **patients with** low-blast AML ~~patients, all CR includes both complete remission (CR) and complete remission with incomplete count recovery (CRi)~~**, composite CR + CRi, CR as well as CRi will be analyzed**.

~~**Overall Survival**~~

~~OS will be calculated from date of randomization to the date of patient death due to any cause. Patients without documented death at the time of the analysis will be censored at the date that the patient was last known to be alive. Stratified log-rank test will be used to compare OS between the 2 treatment arms. Hazard ratios, along with the 2-sided 70% and 95% CIs will be estimated using the unadjusted stratified Cox model. The proportional hazard assumptions will be examined and sensitivity analysis will be conducted if appropriate. Kaplan-Meier curves and Kaplan-Meier medians (if estimable), together with the 70% and 95% CIs, will be calculated for each treatment group.~~

EFS

The analysis of EFS, will be based on patients with HR MDS/CMML and the ITT population separately.

For patients with HR MDS/CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death. EFS is defined as the time from randomization to the occurrence of an event. Unstratified log-rank test will be used to compare EFS between the 2 arms. The hazard ratios along with the 2-sided 95% CIs will be estimated using the unadjusted, unstratified Cox model. The proportional hazard assumptions will be examined and sensitivity analysis will be conducted if appropriate. The Kaplan-Meier survival curves and Kaplan Meier medians (if estimable), along with the 95% CIs, will also be provided for each treatment group.

Six-Month and One-Year Survival Rate

Kaplan-Meier estimates and the ~~70% and~~ 95% CIs of 6-month and 1-year survival rates will be provided based on **patients with HR MDS/CMML** and the ITT population **separately**.

Time to AML Transformation

Time to AML transformation is defined as time from randomization to documented AML transformation. This definition only applies to **patients with** HR MDS and CMML ~~patients~~, so this analysis will only

be carried out in this subgroup. Patients who died before progression to AML will be censored. ~~Stratified~~ **Unstratified** log-rank test will be used to compare time to AML transformation between the 2 arms. Hazard ratio and its 2-sided ~~70% and~~ 95% CI will be calculated using the ~~stratified~~ **unstratified** Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the ~~70% and~~ 95% CIs, will be calculated for each treatment group.

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

CR/CR +~~PR~~ **PR (composite CR + PR for patients with low-blast AML)**/overall response**/CR (not including CRi) in low-blast AML** calculations will be based on the response-evaluable population **of patients overall, the response-evaluable patients with HR MDS/CMML, and the response-evaluable patients with low-blast AML, if appropriate.**

The number and percentage of patients who achieved CR/CR~~+PR~~ **PR (composite CR + PR for patients with low-blast AML)**/overall response (CR+PR+HI for patients with HR MDS/CMML, **composite** CR + PR for patients with low-blast AML)**/CR (not including Cri) in low-blast AML**, respectively, will be summarized by treatment group. CR rate/CR + PR rate **(composite CR + PR for patients with low-blast AML)**/overall response rate**/CR rate (not including CRi) in low-blast AML between the 2 treatment arms**, respectively, will be ~~tested~~ **compared** using the ~~stratified~~ **unstratified** Cochran-Mantel-Haenszel (CMH) chi square test. The ~~CMH chi-square test p-value, the~~ relative risk with its 2-sided ~~70% and~~ 95% CI will be calculated. The absolute rate difference will be provided with its ~~70% and~~ 95% CI.

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

The number and percentage of patients who achieved CR/CR~~+PR~~ **PR (composite CR + PR for low-blast AML)**/overall response (CR + PR + HI for patients with HR MDS/CMML, **composite** CR + PR for patients with low-blast AML)**/CR (not including CRi) in low-blast AML** by Cycle 4, respectively, will be summarized by treatment group. CR rate/CR~~+PR~~ **+ PR (composite CR + PR for patients with low-blast AML)** rate/overall response rate**/CR rate (not including CRi) in low-blast AML** by Cycle 4 **between the 2 treatment arms**, respectively,

will be ~~tested~~ **compared** using the ~~stratified~~ **unstratified** ~~Cochran-Mantel-Haenszel (~~CMH~~)~~ chi-square test. The ~~CMH chi-square test p-value, the~~ relative risk with its 2-sided ~~70% and~~ 95% CI will be calculated. The absolute rate difference will be provided with its ~~70% and~~ 95% CI.

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

Calculations of duration of responses will be based on ~~the response-evaluable population~~ **responders from the overall patient population, responders from patients with HR MDS/CMML, and responders from patients with low-blast AML, if appropriate**.

Duration of CR/CR + PR/overall response (CR +PR + HI for patients with HR MDS/CMML, CR + **CRi +** PR for patients with low-blast AML)**/CR (not including CRi) in low-blast AML**, respectively, will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates.

Time to First CR or PR

Analysis of time to first CR **(composite CR for patients with low-blast AML)** or PR will be based on the response-evaluable **patients with HR MDS/CMML and the response-evaluable** population **for the overall patient population separately**.

Time to first CR or PR is defined as time from randomization to first documented CR or PR, whichever occurs first. ~~Stratified~~ **Unstratified** log-rank test will be used to compare time to first CR or PR between the 2 arms. Hazard ratio and its 2-sided ~~70% and~~ 95% CI will be calculated using the ~~stratified~~ **unstratified** Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the ~~70% and~~ 95% CIs, will be calculated for each treatment group.

Time to Subsequent Therapy

Analysis of time to subsequent therapy will be based on **patients with HR MDS/CMML and** the ITT population **separately**.

~~Stratified~~ **Unstratified** log-rank test will be used to compare time to subsequent therapy between the 2 arms. Hazard ratio and its 2-sided ~~70% and~~ 95% CIs will be calculated using ~~stratified~~ **unstratified** Cox model. Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), together with the ~~70% and~~ 95% CIs will be calculated for ~~reach~~ **each**

treatment group.

Rate of Transfusion Independence

Analysis of RBCs and platelet-transfusion independence will be based on **patients with HR MDS/CMML and** the ITT population **separately**.

A patient is defined as RBC or platelet-transfusion independent if he/she receives no RBC or platelet transfusions for a period of at least 8 weeks [13,73]. Rate of transfusion independence is defined as number of patients who become transfusion independent divided by the number of patients who are transfusion dependent at Baseline. The number of patients who are transfusion dependent/independent at Baseline and post Baseline, as well as rate of transfusion independence, will be summarized by treatment group. Rate of transfusion independence **between the 2 treatment arms** will be ~~tested~~ **compared** using ~~stratified~~ **unstratified** CMH test. ~~P values and~~ **The relative risk with its** 2-sided ~~70% and~~ 95% CIs ~~of the relative risk~~ will be provided.

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

Analysis of number of inpatient hospital admissions related to HR MDS, CMML, or AML will be based on **patients with HR MDS/CMML and** the ITT population **separately**. Inpatient hospital admission data will be collected through transformation to AML (**patients with** HR MDS/CMML ~~patients~~) or disease progression (**patients with** low-blast AML ~~patients~~) or until initiation of subsequent therapy (all patients), whichever occurs first.

The number and percentage of patients who have any hospitalizations related to HR MDS, CMML, or AML will be summarized by treatment group. The absolute rate difference will be provided with its ~~70% and~~ 95% CI.

Time to PD, Relapse, or Death

Analysis of time to PD, relapse, or death will be based on **patients with HR MDS/CMML and** the ITT population **separately**.

Time to PD, relapse, or death is defined as the time from randomization until disease progression, or relapse, or death due to any cause, whichever occurs first. ~~Stratified~~ **Unstratified** log-rank test will be used for comparison between the 2 arms. The hazard ratios along with the 2-sided ~~70% and~~ 95% CIs will be estimated using the unadjusted ~~stratified~~ **unstratified** Cox model. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), along with the ~~70% and~~ 95% CIs, will also be provided for each treatment group.

Rationale for Change: Clarify the definitions of CR and composite CR (CR plus CRi) in patients with low-blast AML, provide data on both HR MDS/CMML and the ITT

populations, and update the analyses accordingly.	
Change 14: Clarify populations for analyses of health-related quality of life.	
Primary change occurs in 8.1.7 Analyses of Health-related Quality of Life	
Initial wording:	Analyses of HRQOL data for EORTC-QLQ-C30 and EQ-5D-5L will be performed using the ITT population; and for QOL-E data, the American English-speaking US patient population only will be used.
Amended or new wording:	Analyses of HRQOL data for EORTC-QLQ-C30 and EQ-5D-5L will be performed ~~using~~ **based on patients with HR MDS/CMML and** the ITT population **separately**; and for QOL-E data, the American English-speaking US patient population only will be used.
Rationale for Change: Clarification of populations for analyses.	
Change 15: Specify CCI [redacted]	
Primary change occurs in Section 8.1.8 Pharmacokinetics/Pharmacodynamics/Biomarkers	
Initial wording:	CCI [redacted]
Amended or new wording	CCI [redacted]

CCI [redacted]

Rationale for Change: CCI [redacted]

Change 16: Delete the exclusion of CYP3A inhibitors from the concomitant medicines table during administration of pevonedistat therapy.

Primary change occurs in Section 15.6 Excluded CYP3A Inducers

Initial wording:

15.6 Excluded CYP3A Inhibitors and Inducers

Use of strong CYP3A inhibitors or inducers listed in Table 15.a should be avoided during pevonedistat therapy. Note that HIV medications that are strong CYP3A inhibitors or inducers are not included in this list because HIV-positive patients are excluded from study participation.

Table 15.a In Vivo Inhibitors or Inducers of CYP3A

Strong Inhibitors (5-fold increase in AUC)	Strong Inducers (≥80% decrease in AUC)
Clarithromycin	Carbamazepine
Itraconazole	Phenytoin
Ketoconazole	Phenobarbital
Nefazodone	Primidone
Voriconazole[a]	Rifabutin
Posaconazole	Rifampin
Telithromycin	Rifapentine
Conivaptan	St. John's wort

a Permitted only if the patient's clinical condition requires the use of an azole antifungal agent. The patient may receive voriconazole 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), Friday (Day 5) schedule, then voriconazole 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.

Amended or new wording:

15.6 Excluded CYP3A ~~Inhibitors and~~ Inducers

Use of strong CYP3A ~~inhibitors or~~ inducers listed in Table 15.a should be avoided during pevonedistat therapy. ~~Note that HIV medications that are strong CYP3A inhibitors or inducers are not included in this list because HIV-positive patients are excluded from study participation.~~

Table 15.a In Vivo ~~Inhibitors or~~ Inducers of CYP3A

~~**Strong Inhibitors (5-fold increase in AUC)**~~	**Strong Inducers (≥80% decrease in AUC)**
~~Clarithromycin~~	Carbamazepine
~~Itraconazole~~	Phenytoin
~~Ketoconazole~~	Phenobarbital
~~Nefazodone~~	Primidone
~~Voriconazole~~[a]	Rifabutin
~~Posaconazole~~	Rifampin
~~Telithromycin~~	Rifapentine
~~Conivaptan~~	St. John's wort

~~a Permitted only if the patient's clinical condition requires the use of an azole antifungal agent. The patient may receive voriconazole 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), Friday (Day 5) schedule, then voriconazole 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.~~

Rationale for Change: To reflect recent data that indicates moderate or strong CYP3A inhibitors do not affect pevonedistat exposures.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	27-Jul-2018 18:09 UTC
	Clinical Science Approval	27-Jul-2018 20:08 UTC
	Clinical Science Approval	30-Jul-2018 19:56 UTC