NCT03238248

CLINICAL STUDY PROTOCOL

VICC HEM 16146

***PevAz**: A phase II trial of **Pev**onedistat and **Az**acitidine in MDS or MDS/MPN patients who fail primary therapy with DNA methyl transferase inhibitors*

Indication: Myelodysplastic syndrome and myelodysplastic/myeloproliferative overlap syndromes

Phase: II

Protocol History

Original	29 August 2016
Version 1.02	2 March 2017
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PROTOCOL SUMMARY

Study Title:

PevAz: a phase II trial of Pevonedistat and Azacitidine in MDS or MDS/MPN patients who fail primary therapy with DNA methyltransferase inhibitors (DNMTi)

Phase: II

Number of Patients:

A total sample size of 71 patients is anticipated.

Study Objectives

Primary

- To compare survival of patients treated with a combination of pevonedistat and azacitidine after failure of DNA methyltransferase inhibitors (DNMTi) to historical survival for patients with relapsed/refractory myelodysplastic syndrome (MDS) or myelodysplastic/ myeloproliferative overlap syndromes (MDS/MPN) who are ineligible for hematopoietic stem cell transplant (HSCT)

Secondary

- To determine the rate of hematologic improvement (HI) in patients with relapsed/refractory MDS or MDS/MPN treated with pevonedistat and azacitidine after DNMTi failure
- To determine the complete remission (CR) and marrow CR rates in patients with relapsed/refractory MDS or MDS/MPN treated with pevonedistat and azacitidine after DNMTi failure
- To determine the reduction of bone marrow blasts in patients with relapsed/refractory MDS or MDS/MPN treated with pevonedistat and azacitidine after DNMTi failure

Tertiary/Exploratory

- To correlate the mutation burden in patients with relapsed/refractory MDS or MDS/MPN with response to treatment with pevonedistat and azacitidine
- To correlate genomic aberrations with rate of response and survival in relapsed/refractory MDS or MDS/MPN patients treated with pevonedistat and azacitidine
- To measure the effect of pevonedistat treatment in combination with azacitidine on quality of life in patients with relapsed/refractory MDS or MDS/MPN
- To define epigenetic biomarkers for pevonedistat use in relapsed/refractory MDS or MDS/MPN

Overview of Study Design:

This is a single-arm, open-label, phase II study of pevonedistat and azacitidine ("PevAz") in patients with relapsed and/or refractory MDS or MDS/MPN.

Bone marrow biopsy and aspirate will be performed before initiating study treatment to confirm the diagnosis and to obtain biospecimens for exploratory research.

All patients are scheduled to initiate treatment at 75 mg/m^2 azacitidine + 20 mg/m^2 pevonedistat.

On Days 1, 2, 3, 4 and 5 of each 28-day cycle, each patient is scheduled to receive azacitidine at 75 mg/m^2 either by subcutaneous (SC) or intravenous (IV) route of administration. Each site will obtain azacitidine from commercial supply.

On Days 1, 3 and 5 of each 28-day cycle, each patient is scheduled to receive pevonedistat at 20 mg/m^2 by iv. The study will supply pevonedistat to each site.

Treatment will continue every 28 days until disease progression, unacceptable toxicity, revocation of consent, or until 12 months of active treatment have been received.

Adverse events and quality of life will be assessed at least monthly. Bone marrow response will be evaluated after 2 and 6 cycles of therapy are completed, at the time of suspected disease progression and at the end of study treatment. Survival assessments will continue at least every 3 months for up to one year after completion of therapy.

This study will be conducted at 5-6 U.S. medical centers.

Study Population:

Inclusion criteria:

1. Signed and dated voluntary written informed consent 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.
2. Male or female ≥ 18 years of age.
3. Morphologically confirmed diagnosis of MDS or MDS/MPN in accordance with WHO diagnostic criteria. (See Section 11.1)
4. ECOG performance status of 0, 1 or 2. (See Section 11.2)
5. Expected survival ≥ 3 months after consenting.
6. Refractory/relapsed disease following DNMTi failure. Refractory disease defined as either 1) failure to achieve an objective response after at least 4 cycles of DNMTi therapy, or 2) failure to achieve an objective response with clear progressive disease on bone marrow biopsy after at least 2 cycles of DNMTi therapy. Relapsed disease is defined as having progressive disease after achieving an objective response after at least 2 cycles of DNMTi therapy. Progressive disease and response criteria are defined for MDS in Section 11.3 and for MDS/MPN in Section 11.4.
   Previous DNMTi therapy may include 5'azacitidine, decitabine, or DNMTi therapy currently in clinical trials (e.g. SGI-110 (guadecitabine), ASTX727 or CC-486).To be considered DNMTi treatment failure, during each prior treatment cycle, patients must have received equivalent to minimum dosing of:
   - decitabine 15mg/m^2 daily x 5 days, or
   - 5'azacitidine 50mg/m^2 IV/SC daily x 5 days,
   - SGI-110 (guadecitabine) 60mg/m^2 SC daily x 5 days, or
   - oral DNMTi therapy with ASTX727 20/100mg daily x 5 days, or
   - oral DNMTi therapy with CC-486 200mg daily x 14 days.
7. Recovery to ≤ Grade 1 or baseline of any toxicity due to prior systemic treatments, excluding alopecia.
8. Patient consent to collection of fresh bone marrow biopsy and aspirate for exploratory research obtained from a procedure performed no more than 28 days prior to initiating treatment on Cycle 1, Day 1. Requirement for bone marrow biopsy may be waived with approval of the study chair in the event that a bone marrow biopsy cannot be obtained.
9. Clinical laboratory values as specified below:
   - Serum albumin > 2.7 g/dL
   - Total bilirubin ≤ 1.5 x ULN
   - ALT and AST ≤ 2 x ULN
   - Calculated creatinine clearance ≥ 50 mL/min (per the Cockcroft-Gault formula) (See Section 11.5)
   - WBC ≤ 50,000/μL (use of hyroxyurea is permitted)
10. Hgb <8g/dL should be transfused to provide adequate tissue perfusion as per the discretion of the investigators and local practice. Rechecking Hgb level prior to start on Cycle 1 Day 1 is not necessary as long as patients do not have inadequate oxygenation, underlying cardiopulmonary compromise, and/or any other reason deemed clinically significant to delay therapy per the investigator.
11. Women of childbearing potential must have a negative serum pregnancy test; and additionally agree to simultaneously use at least 2 methods of effective contraception (see Section 11.6) or abstain from heterosexual intercourse from the time of signing consent, and until 4 months after patient's last dose of protocol-indicated treatment. Periodic abstinence (e.g. calendar,

ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.
WOCBP are defined as those not surgically sterile or not post-menopausal.
If a female patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for at least 1 year in the absence of an alternative medical cause, then patient will be considered a female of childbearing potential. Postmenopausal status in females under 55 years of age should be confirmed with a serum FSH level within laboratory reference range for postmenopausal women.

12. Men, even if surgically sterilized (i.e. status post-vasectomy), who are sexually active with WOCBP must agree to follow instructions for effective barrier contraception (see Section 11.6) from the time of signing consent and until 4 months after last dose of protocol-indicated treatment. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.

Exclusion criteria:

1. Diagnosis of acute myeloid leukemia (i.e. ≥ 20% peripheral or marrow blasts).
2. Any HSCT within 6 months prior to signing informed consent.
3. Any patient who is eligible for HSCT at the time of study screening.
4. Clinically significant graft versus host disease (GVHD) or GVHD requiring initiation of treatment or treatment escalation within 21 days, and/or > Grade 1 persistent or clinically significant non-hematologic toxicity related to HSCT
5. Any previous treatment with pevonedistat or other NEDD8 inhibitor.
6. Treatment with any investigational products within 14 days before the first dose of protocol-indicated treatment.
7. Systemic antineoplastic therapy or radiotherapy within 14 days before the first dose of any study drug.
8. Major surgery requiring general anesthesia within 14 days before the first dose of any study drug or a scheduled surgery during study period. (Placement of a central line or port-a-catheter is acceptable within this time frame and does not exclude the patient.)
9. Treatment with clinically significant metabolic CYP3A inducers within 14 days before the first dose of study drug. Clinically significant CYP3A inducers are not permitted during the study. (See Section **Error! Reference source not found.**)
10. Prolonged QTc interval > 500 msec, calculated according to Fredericia's formula.
11. Known cardiopulmonary disease defined as having one or more of the following:
    - Uncontrolled high blood pressure (i.e. systolic > 180 mmHg or diastolic > 95 mmHg);
    - Symptomatic cardiomyopathy;
    - Ischemic heart disease; Patients with acute coronary syndrome, myocardial infarction, and/or revascularization (e.g. coronary artery bypass graft, stent) within 6 months of first dose of study drug are excluded; Patients with a history of ischemic heart disease who have had revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll;
    - Arrhythmia (e.g. history of polymorphic ventricular fibrillation or torsade de pointes). Patients with symptomatic atrial fibrillation (Afib) incompletely controlled medically, or controlled by device (e.g. pacemaker) or by ablation in the past 6 months are excluded. However, patients with stable AFib for a period of at least 6 months, whose Afib is controlled with medication, or who have a history of paroxysmal AFib are permitted to enroll;
    - Implantable cardioverter defibrillator;

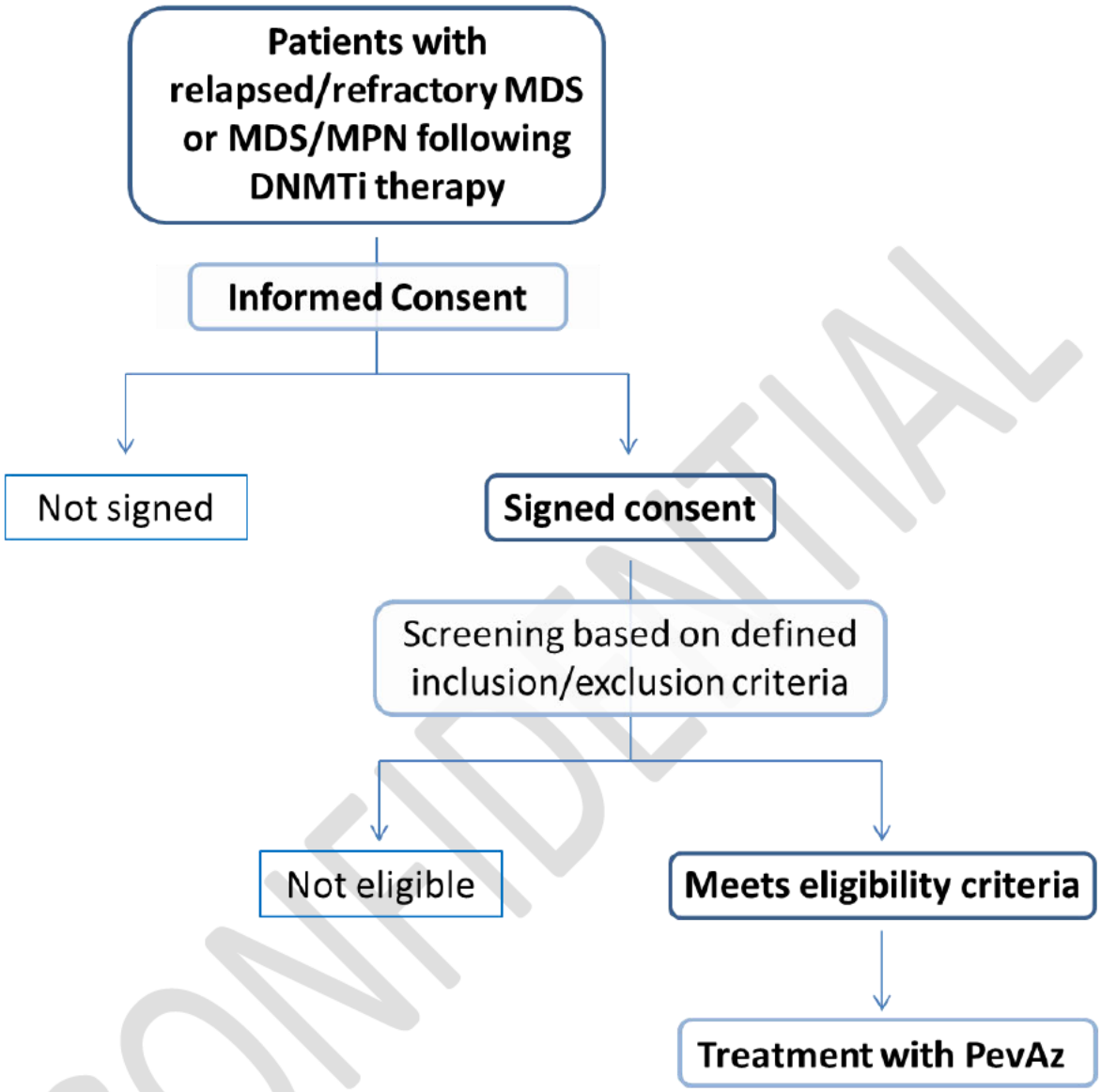
- Congestive heart failure (New York Heart Association [NYHA] Class III or IV; or Class II with a recent decompensation requiring hospitalization or referral to a heart failure clinic within 4 weeks before screening),
- Moderate to severe aortic and/or mitral stenosis or other valvulopathy (ongoing). Mild regurgitation is not excluded;
- Pulmonary hypertension.

12. Female patients who are both lactating and breastfeeding, who have a positive serum pregnancy test during screening, or who plan to become pregnant while in the trial or within 90 days after receiving protocol-directed treatment.
13. Active uncontrolled infection. Patients with infection under active treatment and controlled with antibiotics are not excluded.
14. Known Childs class B or C hepatic cirrhosis or severe pre-existing hepatic impairment.
15. Known hepatitis B surface antigen seropositivity or known or suspected active hepatitis C infection. Note: Patients who have isolated positive hepatitis B core antibody (i.e. in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load.
16. Known human immunodeficiency virus (HIV) seropositivity.
17. Any serious concurrent condition that could, in the investigator's opinion, significantly interfere with completion of study procedures or protocol compliance.
18. 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).
19. 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).

Duration of Study:

Overall enrollment is expected to last approximately 12 months. It is anticipated that patients will receive study treatment until progression of disease, unacceptable toxicity, revocation of consent, or until 12 months of active treatment have been received. Patients achieving CR/PR/HI will be allowed to continue study therapy upon discussion with the study chair

STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

Protocol Activities **1 Cycle = 4 weeks (28 days)**	**Screening (Day -21 to Day -1)**	**CYCLES ≥ 1**					**CYCLE 1**	**Post-Treatment**		
		Day 1 (± 3 d)[p]	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 15[q]**	**EOT (≤ 14d)[r]**	**Follow-Up (30d + 14d after last study dose)[s]**	**Survival[t]**
Clinical Assessments										
Consent, Baseline Characteristics & Eligibility[a]	X									
Physical Examination[b]	X	X					X	X	X	
Spleen/Liver Assessment[b] **(MDS/MPN only)**		c1d1, c3d1 c7d1						X		
ECOG Performance Status	X	X						X	X	
Height	X									
Weight[c]	X	X						X	X	
Vital signs	X	X					X	X	X	
Surveillance for Adverse Events[d]	X	X					X	X	X	
Review of Concomitant Medications[e]	X	X						X	X	
Quality of Life Assessment[f]	X	X						X	X	
Survival Follow-Up										X
Laboratory Assessments										
Hematology and Blood Chemistry[g]	X	X[v]		X		X	X	X	X	
Coagulation[h]	X	X[h]								
Pregnancy Test[i]	X	X						X		
12-lead ECG[j]	X	X[j]				X[j]		X		
Biospecimen Collections										
Fresh Bone Marrow Biopsy & Aspirate[k,l]	X	c3d1 c7d1						EOT/PD		
Pharmacogenetic/ Pharmacodynamic Blood[m]	X	c3d1 c7d1						EOT/PD		
Treatment										
Azacitidine injection or infusion[n]		X	X	X	X	X				
Pevonedistat infusion[o]		X		X		X				

Abbreviations: c cycle, d days, ECOG Eastern Cooperative Oncology Group, ECG electrocardiogram, EOT end of treatment, PD progressive disease

Notes:

a. Informed consent must be obtained before any study-specific screening assessments are performed. Screening assessments are to be performed within 21 days prior to Day 1 of Cycle 1 unless otherwise noted (e.g. see immediately below paragraph, regarding MDS and MDS/MPN testing). Assessments performed as standard-of-care within the screening window may be used for screening. Baseline characteristics include but are not limited to: demographics, medical and surgical history, morphology and extent of disease burden, prior anti-cancer treatment, and documentation of MDS or MDS/MPN status as resulted from an acceptable local or designated lab.

   Prior to initiating treatment, all patients must have morphologically confirmed diagnosis of MDS or MDS/MPN. After informed consent, an expanded screening window of up to 28 days prior to Cycle 1, Day 1 is applicable for any necessary disease-specific testing (i.e. if results not already available). A patient without documentation from an acceptable local or designated lab of eligible MDS or MDS/MPN status will not be eligible to enroll in the study.

b. A complete physical examination will be done at Screening and at the End-of-Treatment or 30-day Follow-Up visit. At other visits, a targeted physical examination may be done including assessment of the lungs, heart, abdomen and other body areas deemed appropriate by the treating physician or qualified designee. For MDS/MPN patients only, physical examination on Day 1 of Cycles 1, 3 and 7 and at the EOT visit should include assessment of palpable hepatosplenomegaly indicative of extramedullary hematopoiesis. Cycle 1 Day 1 and either EOT or Follow-Up exams must be done by a physician; at other time points, physical exams may be conducted either by a physician or other qualified designee (e.g. nurse practitioner).

c. Weight at Screening; on Day 1 of each cycle; and at EOT and Follow-up visits. Each dose of azacitidine and pevonedistat must be adjusted if patient's body weight changes > ±10%.

d. Review and capture of all concomitant medications will be performed as indicated. Concomitant medications are defined as any prescription medications or over-the-counter preparations used by a patient within 14 days before signing informed consent and continuing through the 30-day Follow-Up study visit. After signing the informed consent, adverse events will be collected as detailed in protocol Section 8.

e. Adverse events will be reviewed on Day 1 of each cycle, on Cycle 1 Day 15, and at the End of Treatment and Follow-Up visits. All adverse events will be recorded from the time of informed consent at least until 30 days after a patient's last azacitidine or pevonedistat treatment (whichever occurs last) or until initiation of another anti-cancer therapy – whichever occurs first.

f. Patient symptoms and quality of life will be assessed using the FACT-Leu Questionnaire (Functional Assessment of Cancer Therapy – Leukemia available through www facit.org) for MDS patients or the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS) for MDS/MPN patients; at screening, on Day 1 of each cycle, at EOT and Follow-Up visits

g. Hematology and Blood Chemistry will be required on Days 1, 3 and 5 of cycles 1-12. If treatment with pevonedistat and azacitidine is continued beyond 12 cycles, due to continued objective response and/or clinical benefit, then Hematology and Blood Chemistry frequency will be at the discretion of the treating investigator in subsequent cycles (i.e. cycles ≥13). Hematology includes white blood cell count with differential, hemoglobin, hematocrit, and platelet count. If disease progression or hematologic toxicity is suspected, frequency may be increased as clinically indicated to include additional evaluations between scheduled assessments. Blood Chemistry to include sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.

h. Coagulation (to include PT and aPTT) will be assessed during screening and on Cycle 2 Day 1. Additional coagulation tests may be performed as clinically warranted.

i. Serum pregnancy test for women of childbearing potential (WOCBP) will be required within 72 hours prior to receiving the first dose of protocol-indicated treatment. Serum or urine pregnancy test should be performed on Day 1 of each subsequent cycle and at EOT for WOCBP. WOCBP are defined as those not surgically sterile or not post-menopausal (i.e. if a female patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for 12 months in the absence of an alternative medical cause, then patient will be considered a WOCBP). Postmenopausal status in females under 55 years of age should be confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women (if a patient's postmenopausal status is considered for childbearing potential and study-required contraception).

j. One standard 12-lead electrocardiogram (ECG) using local site equipment will be performed at screening and at the EOT. During study treatment, one standard 12-lead ECG using local site equipment will be performed to evaluate for arrhythmia post-treatment on Days 1 and 5 of Cycles 1 and 2. Additional ECGs as clinically indicated.

k. In addition to bone marrow tissue (archival or fresh) necessary for baseline MDS or MDS/MPN eligibility analysis, additional FRESH bone marrow biopsy and aspirate is also REQUIRED at baseline for exploratory research. Requirement for bone marrow biopsy may be waived with approval of the study chair in the event that a bone marrow biopsy cannot be obtained.

   Tissue shall be considered "fresh" when it is obtained from a procedure performed at the study site no more than 28 days before treatment on Cycle 1, Day 1.

   Patients who consent to undergo fresh bone marrow biopsy and aspirate prior to initiating study treatment, but whose disease is deemed inaccessible (or insufficient) to a reasonably safe marrow biopsy and aspirate, may be allowed to enroll upon discussion with and approval by the study chair (if otherwise eligible and with known MDS or MDS/MPN status).

   Prior to initiating treatment, a patient's screening team must have documentation that fresh bone marrow biopsy and aspirate has been performed and reasonable attempt made to obtain biospecimens for exploratory research. (Provided that the diagnosis of MDS or MDS/MPN is not in question, waiting for histological analysis or confirmation that acquired specimens are known to contain tissue sufficient for exploratory analysis is not a requirement prior to initiating study treatment.)

l. Fresh bone marrow biopsy and aspirate are required at Baseline (i.e. obtained from a procedure performed no more than 28 days prior to initiating treatment on Cycle 1, Day 1); prior to treatment on Cycle 3, Day 1 and Cycle 7, Day 1 (acceptable windows up to 7 days prior to c3d1 & c7d1 treatment); and at End-of-Treatment ($\leq$ 14 days after the decision was made to discontinue study treatment). Core biopsy and aspirate are to be collected both for assessment of disease response, as well as for correlative research. Requirement for bone marrow biopsy may be waived with approval of the study chair in the event that a bone marrow biopsy cannot be obtained.

   If a patient discontinues study treatment for reason other than progressive disease confirmed by marrow procedure (e.g. due to adverse event), then every effort should be made to obtain fresh bone marrow biopsy and aspirate samples to evaluate response and to obtain biospecimens for exploratory research.

   If progressive disease is suspected between scheduled study bone marrow examinations (e.g. due to suspicious peripheral blood counts), fresh bone marrow biopsy and aspirate samples must be collected to evaluate for progressive disease and to obtain bone marrow aspirate for research purposes. If

progressive disease is confirmed in that procedure and the patient will terminate the study as a result, it can be considered synonymous with their end of treatment evaluation.

Also, at any time during the study, if additional bone marrow biopsy/aspirates are performed as standard-of-care, then a sample of the marrow aspirate, if available, may be requested for research purposes.

On day of a marrow procedure, matching peripheral Pharmacogenetic (PG) and Pharmacodynamic (PhD) blood samples referenced below in Note 10 are to be drawn PRIOR to the marrow biopsy/aspirate procedure and ideally coincident with Hematology and Blood Chemistry specimens also scheduled to be collected on those days.

m. PG and PhD blood samples for research are to be obtained at Baseline (i.e. on same-day prior to the fresh baseline bone marrow biopsy and aspirate); Pre-Dose prior to scheduled azacitidine treatment: on Day 1 of Cycles 3 and 7; and at the End-of-Treatment visit. Note: on Day 1of Cycles 3 and 7 and at the EOT visit, blood samples for research should be obtained at a single time point prior to scheduled bone marrow procedure and as such, may occur within the same window as the bone marrow biopsy and aspirate procedure (e.g. acceptable windows up to 7 days prior to c3d1 & c7d1 treatments and ≤ 14 days after the decision was made to discontinue study treatment for the EOT assessment). After the EOT visit, if a disease progression biopsy and/or aspirate is later conducted (and not previously obtained at the EOT visit), then an additional PG/PhD blood sample should be obtained on the same-day as the progression procedure; as well as at any time during the study, if additional bone marrow biopsy/aspirates are performed standard-of-care.

n. All patients are scheduled to receive azacitidine on Days 1, 2, 3, 4, and 5 of each 28-day cycle. When both drugs are administered on Days 1, 3 and 5, azacitidine will be administered BEFORE pevonedistat. Azacitidine may be administered either by subcutaneous injection, or intravenous infusion: Before treating a first patient, the local principal investigator at each participating site will advise the coordinating center if the participating site will administer azacitidine by subcutaneous (SC) injection or by intravenous (IV) infusion (see Section 6.1.1 for additional details). Site will be asked to make efforts to consistently treat patients via either SC or IV route as chosen by each site prior to enrolling the first patient. Understandably, there will be exceptions and need to change route of administration for some patients (eg injection site reactions with SC). Each site will obtain azacitidine from commercial supply.

o. All patients are scheduled to receive pevonedistat by intravenous infusion on Days 1, 3 and 5 of each 28 day cycle. Pevonedistat will be administered AFTER azacitidine (on days when both drugs are administered). The study will provide pevonedistat to each site.

p. On Cycle 1, Day 1: Hematology and Blood Chemistry and Serum Pregnancy Test performed for eligibility screening more than 3 calendar days prior to Cycle 1, Day 1 must be repeated to confirm adequate organ function prior to initiating study-indicated treatment. Physical exam, Weight, Hematology and Blood Chemistry, and Pregnancy test need not be repeated if already completed within 3 calendar days prior to first dose of azacitidine/pevonedistat. For example, if screening labs and assessments are performed on a Friday and are within range, those labs and assessments would not need to be repeated if the patient receives the first dose of protocol-indicated treatment (e.g. Cycle 1 Day 1) on or before the following Monday. Beginning with Cycle 2, in order to accommodate scheduling, Day 1 initiation of a new cycle may occur with flexibility of ± 3 days.

q. On Cycle 1, Day 15: Physical exam, Vital signs, Surveillance for Adverse Events, and Hematology and Blood Chemistry should be obtained to assess count nadir and need for red blood cell or platelet transfusion. Mid-cycle visits in subsequent cycles are not required by the study, but may be performed if indicated (e.g. if the patient has low counts at baseline or experienced treatment-related cytopenias in cycle 1) at the judgment of the treating investigator.

r. Reasonable effort should be made to complete End-of-Treatment (EOT) procedures on the day it is decided a patient will no longer receive protocol-indicated treatment. The EOT procedures must be completed subsequent to and not later than 14 days after investigator decision to permanently discontinue protocol treatment with azacitidine/pevonedistat (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy.

s. A Follow-up clinic visit is to be completed 30 days (+14 day window) after patient's final treatment with azacitidine or pevonedistat (whichever occurs last). Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities. (Note it is possible that EOT and Follow-Up visit items might both be completed in as few as a single clinic visit.)

   Additionally, for patients who discontinue study treatment for reason other than progressive disease confirmed by marrow procedure (e.g. suspicious peripheral blood counts), please note the study may continue to request results of bone marrow examinations conducted outside of the study, until progressive disease following azacitidine/pevonedistat is ultimately confirmed.

t. Each patient will be followed for survival every 3 months (± 14 days) after patient's final treatment with azacitidine or pevonedistat (whichever occurs last) until death, end of the study, until patient withdraws consent, or for a maximum of 4 years after a patient's final treatment with azacitidine/pevonedistat – whichever comes first. Survival contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

u. Patients with Hgb <8g/dL at screening should be transfused to provide adequate tissue perfusion as per the discretion of the investigators and local practice. Rechecking Hgb level prior to receiving treatment is not necessary as long as patients do not have inadequate oxygenation, underlying cardiopulmonary compromise, and/or any other reason deemed clinically significant to delay therapy per the investigator.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
aCML	atypical BCR-ABL1 negative chronic myeloid leukemia
ADR	adverse drug reaction
AE	adverse event
ALL	acute lymphoblastic leukemia
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
AV	atrioventricular
BCRP	breast cancer resistance protein
BID	bis in die; twice a day
BMT	bone marrow transplant
BSA	body surface area
BUN	blood urea nitrogen
CA	carbonic anhydrase
CBC	complete blood count
CDL	cullin-dependent ubiquitin E3 ligase
Cdt-1	chromatin licensing and DNA replication factor-1
CFR	Code of Federal Regulations
CL_P	plasma clearance
C_{max}	single-dose maximum (peak) concentration
CMML	chronic myelomonocytic leukemia
COPD	chronic obstructive pulmonary disease
CQS	Vanderbilt Center for Quantitative Sciences
CR	complete remission
CRF	case report form
CRi	complete remission with incomplete blood count recovery
CRM	continual reassessment method
CRP	C-reactive protein

Abbreviation	Term
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTSR	Clinical Trial Shared Resource
CV	cardiovascular
CYP	cytochrome P_{450}
DCSI	Development Core Safety Information
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DNMTi	DNA methyltransferase inhibitor(s)
DSMB	data safety and monitoring board
DSMC	Data Safety and Monitoring Committee
EC	Ethics committee
eC_{CR}	estimated creatinine clearance rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment (visit)
FAB	French-American-British
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
FDA	United States Food and Drug Administration
FISH	fluorescence *in situ* hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GUI	graphical user interface
GVHD	graft versus host disease
HEM	Hematology
hERG	human ether-à-go-go related gene
HI	hematologic improvement

Abbreviation	Term
HIF-1α	hypoxia-inducible factor 1 alpha
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	investigational new drug
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IWG	International Working Group
JMML	juvenile myelomonocytic leukemia
K_i	inhibition constant
LFT	liver function test(s)
MDS	myelodysplastic syndrome
MDS/MPN	myelodysplatic syndrome/myeloproliferative neoplasm overlap syndrome
MDS/MPN-U	myelodysplastic syndrome/myeloproliferative neoplasm unclassifiable
MedDRA	Medical Dictionary for Regulatory Activities
MPN	myeloproliferative neoplasm
MPN-SAF	myeloproliferative neoplasm symptom assessment form
MPN-SAF TSS	myeloproliferative neoplasm symptom assessment form total symptom score
MRP2	multidrug resistance-associated protein-2
MTD	maximum tolerated dose
NAE	Nedd8-activating enzyme
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRF2	nuclear factor (erythroid-derived 2)-like 2
NYHA	New York Heart Association
ORR	overall response rate

Abbreviation	Term
PD	progressive disease (disease progression)
PevAz	pevonedistat + azacitidine
PG	pharmacogenetic
P-gp	p-glycoprotein
PhD	pharmacodynamic
PK	pharmacokinetic(s)
PR	partial remission
PT	prothrombin time
QD	*quaque die*; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RA	refractory anemia
RAEB-T	refractory anemia with excess blasts in transformation
RAEB	refractory anemia with excess blasts
RARS	refractory anemia with ringed sideroblasts
RARS-T	refractory anemia with ringed sideroblasts and thrombocytosis
RBC	red blood cell
RNA	ribonucleic acid
RP2D	recommended Phase II dose
SA	sinoatrial
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SRC	Scientific Review Committee
STD	severely toxic dose
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
TI	transfusion independence
Ub	ubiquitin
ULN	upper limit of the normal range
UPS	ubiquitin-proteasome system
US	United States
VICC	Vanderbilt-Ingram Cancer Center
V_z	volume of distribution in the terminal phase
WBC	white blood cells
WGMS	whole genome methylation studies

Abbreviation	Term
WHO	World Health Organization
WOCBP	woman/women of child-bearing potential

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Myelodysplastic Syndromes

Myelodysplastic syndrome (MDS) collectively refers to a heterogeneous group of clonal neoplastic hematopoietic stem cell disorders characterized by dysplastic morphologic features of hematopoietic cells, increased bone marrow cellularity, and peripheral cytopenias[1]. Clinically, MDS manifest with one or more peripheral cytopenias—anemia, neutropenia, and/or thrombocytopenia—of variable severity. Cytopenias in MDS tend to be progressive. Consequently, patients with MDS are at increased risk of transfusion-dependence, severe infection, and/or hemorrhage. Furthermore, MDS may evolve to acute myelogenous leukemia (AML) with dismal outcomes[1,2].

MDS disproportionately affect the elderly. In the United States, there are an estimated 45,000 new cases of MDS annually in patients over 65 years of age[3]. The median age at diagnosis is 75 years, with the highest incidence rate in 80 – 85 year old individuals[3,4].

MDS patients are stratified into low risk, intermediate-1 risk, intermediate-2 risk, and high risk groups, based on karyotype, burden of cytopenias, and blast count according to the International Prognostic Scoring System (IPSS)[5]. A revision of the IPSS (IPSS-R), further discriminates risk by weighting the degree of anemia and thrombocytopenia and percent of bone marrow blasts[6]. While low-risk patients are often expectantly managed with supportive measures such as red blood cell transfusions and/or growth factor support, patients with intermediate or higher risk disease are often treated with disease-modifying deoxyribonucleic acid methyltransferase inhibitors (DNMTi), such as decitabine or 5'azacitidine[7].

Although some specific cytogenetic aberrations and genetic mutations occur with increased frequency in MDS, there is tremendous cytogenetic variability and no one driver mutation has been identified[1]. A common thread, however, is seen with mutations in genes that modify target gene expression by deoxyribonucleic acid (DNA) methylation, histone modification and ribonucleic acid (RNA) splicing. As a result, drugs that target epigenetic modifiers, such as the DNMTi, have become one focus of therapeutic development in MDS[8].

1.1.2 MDS/Myeloproliferative Neoplasm Overlap Syndromes (MDS/MPN)

Myelodysplastic syndrome/Myeloproliferative neoplasm (MDS/MPN) overlap syndromes comprise a World Health Organization (WHO) category of hematopoietic stem cell malignancies sharing morphologic and hematologic features of both MDS and MPN[9]. As characterized by the WHO (2016), these disorders include chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), atypical BCR-ABL1 negative chronic myeloid leukemia (aCML), myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) and myelodysplastic/myeloproliferative neoplasm unclassifiable (MDS/MPN-U)[10].

Similar to MDS, MDS/MPN patients present with peripheral cytopenias and dysplastic hematopoietic cells[9]. However, they also commonly have constitutional symptoms, extramedullary hematopoiesis and symptoms associated with splenomegaly, all of which are relatively uncommon in MDS and more typical of classical MPNs.

MDS/MPN are relatively uncommon and hence have not been rigorously studied. Although mutations in epigenetic modifiers, cell signaling proteins, and transcriptional and RNA splicing machinery have been identified in MDS/MPN, even within a particular subtype of MDS/MPN, genetic heterogeneity exists[11]. As a result, treatment strategies in MDS/MPN are often unrefined and reflective of their clinical similarities to either MDS or MPN.

1.1.3 Pevonedistat

The coordinated balance between synthesis and degradation of proteins is important in most cellular processes, and the ubiquitin-proteasome system (UPS) is responsible for much of the regulated protein turnover in the cell[12]. The UPS maintains cellular homeostasis and impacts many signaling pathways including cell cycle progression and regulation of transcription[13]. This complex, multiprotein system involves distinct enzyme classes that coordinate ubiquitination and mediate ubiquitin-dependent degradation through the proteasome. Proteasome inhibitors have utility in the treatment of multiple myeloma and mantle cell lymphoma[14,15], suggesting that compounds targeting other components of the UPS could prove useful in the treatment of malignancies.

The polyubiquitination reaction involves the coordination of 3 classes of enzymes, E1 (ubiquitin activating), E2 (ubiquitin conjugating), and E3 (ligases). The E3 ligases are multiprotein complexes whose specificity is established by the members of the protein

complex and whose activity is regulated by post-translational modification that include the addition of the ubiquitin-like molecule, neural precursor cell expressed, developmentally down-regulated 8 (Nedd8). Nedd8-activating enzyme (NAE) has been identified as an essential component of the Nedd8 conjugation pathway[16]. The Nedd8 conjugation pathway controls the activity of a subset of UPS E3 ligases (Figure 1-1). Specifically, Nedd8 conjugation to cullin-dependent ubiquitin E3 ligases (CDLs) is necessary for their activity[17]. These ligases control the timely ubiquitination and subsequent degradation of many proteins important for cell cycle progression (p27, cyclin E), DNA damage (Cdt-1), stress response (NRF-2, HIF1α), and signal transduction (phosphorylated IκBα [pIκBα])[18,19].

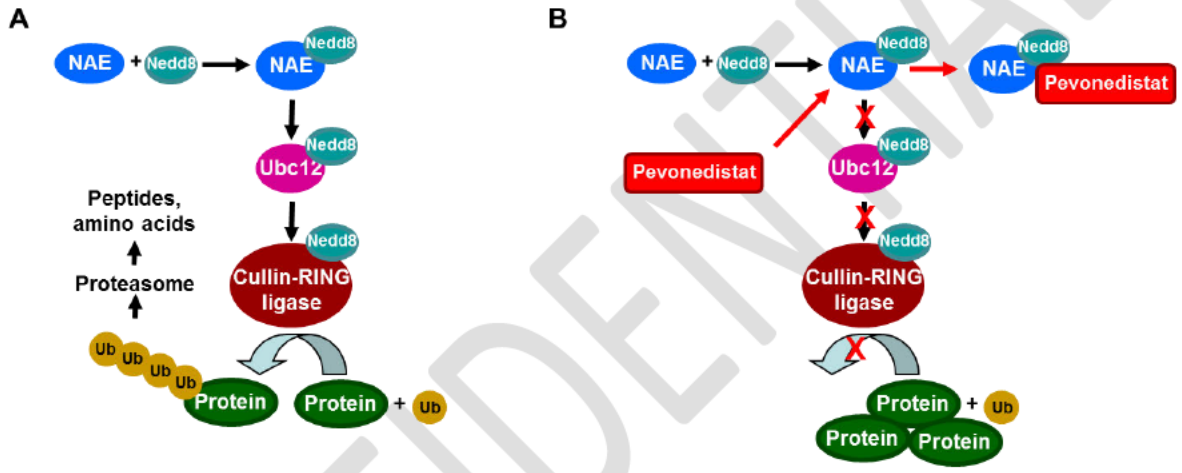

Figure 1-1: Schematic of Polyubiquitination and Inhibition by Pevonedistat
A) Schematic of the polyubiquitination reaction. Nedd8 is a ubiquitin-like protein. In conjunction with Nedd8, the Nedd8-activating enzyme (NAE) is responsible for neddylation of the E2 conjugating enzyme Ubc12, which subsequently activates Cullin-RING ligases by neddylation. The activation of Cullin-RING ligases results in the conjugation of multiple ubiquitin (Ub) moieties to target proteins, leading to their subsequent degradation in the proteasome. B) Pevonedistat inhibits NAE resulting in accumulation of target proteins in the absence of Nedd8-dependent polyubiquitination.

Pevonedistat (also known as TAK-924 and MLN4924) is a first-in-class small molecule inhibitor of NAE under development for the treatment of malignancies. Inhibition of NAE stabilizes a subset of the proteins that are also stabilized by inhibition of the proteasome. Pevonedistat exhibits potent *in vitro* cytotoxic activity against a variety of human tumor-derived cell lines in which cell death was shown to correlate with NAE inhibition[20]. In most cancer cell lines studied, including those derived from lung, colon, and lymphoma tissues, the mechanism of cell death appeared to be a consequence of uncontrolled DNA synthesis in the S phase of the cell cycle followed by a DNA-damage response and induction of cell

death[20] However, in the NF-κB-dependent lymphoma line, OCI-Ly10, apoptosis was observed following a G1 arrest suggesting that there may be multiple consequences of NAE inhibition that lead to cell death depending on the genetic background of the malignant cells[21] Hematologic and nonhematologic xenograft models support that inhibition of NAE activity may target a broad range of tumors.

1.2 Preclinical Experience with Pevonedistat

Detailed information regarding the nonclinical pharmacology and toxicology of pevonedistat is provided in the Investigator's Brochure (IB)[22].

1.2.1 Nonclinical Pharmacology: *In Vitro* Studies

Pevonedistat is a potent and selective inhibitor of NAE activity that binds to the NAE-NEDD8 thioester intermediate and reacts to form a epvonedistat-NEDD8 covalent adduct, which remains noncovalently and reversibly bound to NAE. Pevonedistat was at least 300- and 1800- fold more selective for NAE than for the closely related ubiquitin activating enzyme and sumo activating enzyme, respectively. 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[20,23,24]. When administered in combination with hypomethylating agents azacitidine and decitabine demonstrated synergistic activity in AML cell lines.

Pevonedistat demonstrated pharmacodynamic and antitumor activity in solid tumor, lymphoma, and AML xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route. Antitumor activity of pevonedistat in mice bearing HL-60 and THP-1 tumor xenografts was enhanced by combination treatment with azacitidine. Combination treatment with pevonedistat and docetaxel significantly inhibited tumor growth in the PHTX-02B primary human breast cancer model and the LU1143 primary human squamous non-small cell lung cancer (sqNSCLC) xenograft model. Combination treatment with pevonedistat and carboplatin in both NCI-H69 human small cell lung cancer (SCLC)

xenografts and LU1143 primary sqNSCLC xenografts resulted in significant antitumor activity.

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 800mg/m^2, respectively), pevonedistat was not well tolerated at doses ≥30 mg/kg (≥600mg/m^2). Mortality and/or moribundity were observed within 24 hours postdose as a result of gastrointestinal injury at 40 mg/kg. Increased heart rate was observed at all doses. 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 dose-limiting toxicities (DLTs) in the 2-cycle studies for rats and dogs 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. Pevonedistat was not mutagenic in the bacterial reverse mutation assay (Ames assay).

Pevonedistat was highly bound in whole blood and plasma of mice, rats, dogs, monkeys and humans. No metabolite unique to humans was observed in vitro. In vitro, pevonedistat is predominantly metabolized by the cytochrome P450 (CYP) isozyme 3A4. There is potential for drug drug interactions (DDIs) if pevonedistat is coadministered with drugs that are CYP3A inhibitors or inducers. Pevonedistat is neither an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC_{50} > 100 µM and Ki > 50 µM) nor an inducer of CYP1A2, 2B6, or 3A4/5 (at concentrations up to 30 µM), but is a weak inhibitor of CYP2B6 and 2C8 (IC_{50} = 97.6 and 23.1 µM, respectively). The major elimination pathway of pevonedistat in animals is through the hepatic route. Pevonedistat is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) in Caco 2 cells.

Pevonedistat is also a weak inhibitor of P-gp (IC_{50} = 41.2 to 56.0 µM) and BCRP (IC_{50} = 6.3 µM), but not of MRP2 (IC_{50} > 200 µM). Additionally, pevonedistat is not a substrate for organic anion-transporting proteins (OATPs).

Detailed information regarding the nonclinical pharmacology and toxicology of pevonedistat may be found in the IB[22].

1.3 Clinical Experience with Pevonedistat

The clinical development program of pevonedistat began with 4 phase 1 studies of single-agent pevonedistat at doses ranging from 25 to 278 mg/m^2:

- Study C15001 in patients with solid tumors[25]
- Study C15002 in patients with lymphoma or multiple myeloma[26]
- Study C15003 in patients with AML, high-grade MDS, or acute lymphoblastic leukemia (ALL)[27]
- Study C15005 in patients with melanoma.[28]

In these studies, toxicity involving multi organ failure on C1D1, including serious adverse events (SAEs) of renal, hepatic, and cardiac failure, some with a fatal outcome, was identified at doses equal to or above 110 mg/m^2. On the basis of a comprehensive review of the available phase 1 clinical safety data at the time, a revised risk mitigation strategy, including limiting the dose to no higher than 100 mg/m^2 for single agent administration, was implemented across the pevonedistat program in October 2012. The current understanding of the renal toxicity observed with pevonedistat suggests that it is not a primary event but is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response.

As of January 2017, approximately 240 additional patients were treated in single agent and combination studies, and no C1D1 SAEs of multi-organ failure as described above have been observed. These patients received pevonedistat at a dose of 50 to 100 mg/m^2 as a single agent, a dose of 15 to 30 mg/m^2 in combination with different standard of care therapies, or a dose of 8 mg/m^2 to 20 mg/m^2 in combination with a CYP3A inhibitor. The maximum tolerated dose of pevonedistat administered on Days 1, 3, and 5 for patients with AML in Study C15003 was determined to be 59 mg/m^2.

Current development is focused on pevonedistat in combination with standard clinically available therapies in hematologic malignancies and solid tumors. Ongoing clinical studies are as follows:

- Study C15009 (phase 1b) evaluated the MTD of pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28-day treatment cycle in elderly patients with treatment-naïve AML[29]

- Study C15010 (phase 1b) evaluated the MTD of pevonedistat plus docetaxel, gemcitabine, or the combination of carboplatin and paclitaxel, in patients with solid tumors.[30,31]

- Pevonedistat-1012 (phase 1) is investigating pevonedistat as a single agent and in combination with azacitidine in adult East Asian patients with AML or MDS.

- Pevonedistat-2001 (phase 2) is evaluating the efficacy and safety of pevonedistat plus azacitidine versus single-agent azacitidine in patients with higher-risk MDS (HR MDS), chronic myelomonocytic leukemia, and low-blast acute myelogenous leukemia.

Additionally, Study C15011 (phase 1) is evaluating the effects of CYP3A-mediated inhibition of pevonedistat in patients with solid tumors [drug-drug interaction (DDI) assessment; Part A]. After completion of the DDI assessment portion of the study, patients have the opportunity to continue in the study by participating in Part B (pevonedistat plus docetaxel or the combination of carboplatin and paclitaxel).

As of 22 January 2017, approximately 451 subjects had received pevonedistat in the clinical trials (237 subjects for hematological indications and 214 subjects for solid tumor indications).

1.3.1 Clinical Pharmacokinetics

Population pharmacokinetic (PK) analysis was conducted using data from pevonedistat single-agent studies (C15001, C15002, C15003, and C15005) and pevonedistat in combination with standard-of-care chemotherapy (C15009 and C15010) in patients with solid tumor or hematological malignancies. The database contained 335 subjects contributing 3768 PK observations. Pevonedistat plasma concentration-time profiles were well described by a 2-compartment model with linear elimination. Body surface area (BSA)

was an important predictor of clearance (CL), distributional clearance (Q), and both central and peripheral volumes (Vc and Vp, respectively). For a typical patient with a BSA of 1.73 m^2, an alpha half-life of 1.27 hours and a beta (elimination) half-life of 7.85 hours are estimated. Concurrent administration of carboplatin and paclitaxel decreased the CL of pevonedistat by approximately 44%, translating to an approximately 80% higher pevonedistat exposure (AUC) during coadministration with carboplatin and paclitaxel, consistent with pevonedistat concentration data observed in C15010. Coadministration with azacitidine, gemcitabine, or docetaxel did not appear to affect the CL of pevonedistat. Race, sex, age, tumor type (hematologic vs solid), mild or moderate renal impairment (creatinine clearance [CrCL] ≥30 mL/min), or mildly impaired liver function, to the extent represented in this dataset, had no impact on pevonedistat PK.

In a DDI study (C15011), preliminary data from 26 evaluable patients (13 from the itraconazole arm and 13 from the fluconazole arm) demonstrate that steady-state exposures to fluconazole had a minimal effect on the single-dose IV pevonedistat PK at 8 mg/m^2, while mean systemic exposure to pevonedistat increased by approximately 23% in the presence of itraconazole.

On the basis of these observations, additional patients were enrolled to evaluate the effects of itraconazole on pevonedistat PK at the clinical dose of 20 mg/m^2. Preliminary data from 11 patients who completed protocol-specified dosing and PK evaluations indicated that pevonedistat systemic exposures following IV administration at 20 mg/m^2 in the presence of itraconazole were similar to those in the absence of itraconazole (geometric mean ratio of 0.996 with an associated 90% CI of 0.913 and 1.09). These findings with established moderate and strong CYP3A inhibitor probes indicate a minor contribution of CYP3A to pevonedistat metabolism in humans. On the basis of these results, moderate and strong CYP3A inhibitors and P-gp inhibitors can be used in patients receiving pevonedistat.

For detailed information please consult the current IB.

1.3.2 **Pharmacodynamics**

Preliminary data provide evidence of pathway inhibition downstream of NAE and biological activity of pevonedistat in skin and tumor tissue (solid tumor or AML bone marrow derived blasts) at all doses tested in pharmacodynamic assays. These doses range from 25 to 261 mg/m^2 across the various single-agent, phase 1 pevonedistat trials.

For detailed information please consult the current IB.

1.3.3 Summary of Safety and Efficacy Data Findings Available on Takeda Sponsored Trials

As of 22 January 2017, the clinical development program includes 9 clinical studies in patients with advanced malignancies. Four of the 9 clinical studies are completed phase 1 monotherapy studies (C15001, C15002, C15003, and C15005) and 5 are ongoing phase 1/1b/2 studies (Studies C15009, C15010, C15011, Pevonedistat-1012, and Pevonedistat-2001). Pevonedistat is under development as a component of regimens with azacitidine (Study C15009, Pevonedistat-1012, and Pevonedistat-2001) and with docetaxel or in combination with carboplatin and paclitaxel (Study C15010), and DDIs of pevonedistat with fluconazole or itraconazole (Study C15011). Per the data available as of 22 January 2017, a total of approximately 451 patients received at least one dose of pevonedistat in the overall clinical development program.

For detailed information please consult the current IB.

1.3.3.1 Phase 1 Monotherapy Studies

Overall, 99 patients with advanced solid tumors or melanoma in Study C15001 and Study C15005 were treated with single-agent pevonedistat at doses ranging from 25 to 278 mg/m^2. Common AEs (reported by ≥ 25% of patients in either study) were fatigue, nausea, anemia, decreased appetite, vomiting, diarrhea, myalgia, constipation, arthralgia, dizziness, and peripheral neuropathy. DLTs included increased LFTs, increased creatinine, acute renal failure and acute hepatic failure, hypophosphatemia, and myocarditis. Acute renal failure occurred in 3 patients: 2 patients on Study C15001 at 196 mg/m^2 (1 patient also reported acute hepatic failure); and 1 patient on Study C15005 at 157 mg/m^2, who also reported myocarditis and hyperbilirubinemia. Deaths on study that were considered related to study treatment included multi-organ failure (at 61 mg/m^2 QD × 5 consecutive days and 196 mg/m^2 in Study C15001), disease progression (at 83 mg/m^2 in Study C15001), and renal failure acute (at 209 mg/m^2 in Study C15005).

A total of 128 patients with hematologic malignancies (lymphoma, multiple myeloma, AML, MDS, or ALL) in Study C15002 and Study C15003 were treated with single-agent pevonedistat at doses ranging from 25 to 261 mg/m^2. Common AEs (reported by ≥ 25% of patients in either study) were ALT increased, anemia, AST increased, chills, constipation, decreased appetite, diarrhea, dizziness, dyspnea, fatigue, febrile neutropenia, headache, muscle spasms, myalgia, nausea, peripheral edema, pyrexia, and vomiting. DLTs included increased LFTs, febrile neutropenia, muscle spasms, thrombocytopenia, acute renal failure,

orthostatic hypotension, cardiac failure, rash morbilliform, GI necrosis, hypotension, lactic acidosis, and myocardial ischemia. Deaths on study that were considered related to study treatment (all in Study C15003) included 2 deaths from multi organ failure (at 110 and 147 mg/m^2), 1 from sepsis (at 78 mg/m^2), and 1 from cardiopulmonary failure (at 45 mg/m^2).

The primary aims of the phase 1 monotherapy studies were to establish the safety profile and to determine the MTDs of pevonedistat administered by several different dose schedules in both hematologic and solid tumor settings. While safety, PK, and pharmacodynamic objectives were the primary focus of these studies, disease response was also assessed. A total of 12 patients experienced PRs or better in the phase 1 monotherapy studies.

1.3.3.2 Phase I Combination Studies

1.3.3.2.1 Study C15009

Study C15009 is an ongoing phase 1b study evaluating the MTD of pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28-day treatment cycle in patients 60 years of age or older with treatment naïve AML who are unlikely to benefit from standard induction therapy. As of 22 June 2016, enrollment had completed and 15 patients remained on study. As of 22 January 2017, preliminary data are available for 64 patients enrolled in the study who received at least 1 dose of pevonedistat in combination with azacitidine; these patients had completed a total of approximately 441 cycles, with a median of 4 cycles of treatment In the dose escalation cohorts, 6 patients received 20 mg/m^2 pevonedistat, and 3 patients received 30 mg/m^2. The most common events (reported by ≥ 25% of patients) were constipation (48%), nausea (42%), fatigue (42%), anemia (39%), febrile neutropenia (31%), decreased appetite (30%), thrombocytopenia (28%), and pyrexia (25%). The MTD in this study was determined to be 20 mg/m^2 pevonedistat given on Days 1, 3, and 5, in combination with 75 mg/m^2 azacitidine given on Days 1 through 5, 8, and 9, in 28 day treatment cycles. A total of 45 (70%) patients experienced at least 1 SAE. A total of 13 SAEs were reported for more than 1 patient, including: febrile neutropenia (17 patients); pneumonia (9 patients); AML (6 patients); pyrexia (4 patients); sepsis (3 patients); and acute myocardial infarction, cellulitis, diverticulitis, dyspnoea, embolism, mental status changes, multi-organ failure, and transaminase increased (2 patients each). A total of 21 patients treated with pevonedistat (either 20 mg/m^2 or 30 mg/m^2), discontinued from Study participation because of a TEAE. No other events leading to discontinuation were assessed by study investigators as at least possibly related to study drug treatment. Seventeen on–study deaths had been reported; none assessed as related to study treatment. A total of 31 patients experienced PR or better.

Nineteen patients had a best response of CR, 5 patients had a best response of CRi, and 7 patients had a best response of PR. One patient in the 30 mg/m^2 dose level group achieved a CR; all other responses occurred in patients treated with 20 mg/m^2.

1.3.3.2.2 Study C15010

Study C15010 is an ongoing phase 1b study evaluating the MTD of pevonedistat plus docetaxel, gemcitabine, or a combination of carboplatin and paclitaxel, in patients with solid tumors. As of 22 January 2017, enrollment has completed; 2 patients remain on study. The treatment arms are:

- Arm 1: pevonedistat dosing on Days 1, 3, and 5 with 75 mg/m^2 docetaxel dosing on Day 1 in a 21-day cycle.
- Arm 2 Lead-in: pevonedistat dosing on Days 1, 3, and 5 with AUC6 carboplatin dosing on Day 1 in a 21-day cycle.
- Arm 2: pevonedistat dosing on Days 1, 3, and 5 with paclitaxel dosing on Day 1 and carboplatin dosing on Day 1 in a 21-day cycle. Per protocol, the dose levels for paclitaxel and carboplatin were to be based on the DLTs in the Arm 2 Lead-in cohort; because there were 2 DLTs in the Arm 2 Lead-in cohort doses were set at 175 mg/m^2 paclitaxel and AUC5 for carboplatin.
- Arm 3: pevonedistat dosing on Days 1, 8, and 15 with 1000 mg/m^2 gemcitabine dosing on Day 1, 8, and 15 in a 28-day cycle.

As of 22 January 2017, preliminary data are available for 64 patients enrolled who received at least 1 dose of pevonedistat in combination with standard of care; these patients had completed a total of approximately 366 cycles, with medians ranging from 2 to 6 cycles of treatment across the 4 treatment groups. The starting dose levels for dose escalation and determination of pevonedistat MTD were 15 mg/m^2 for Arm 1 and Arm 2, and 25 mg/m^2 for Arm 3. Overall, the most common AEs (occurring in $\geq$ 25% of patients were fatigue (58%), nausea (50%), anemia (41%), diarrhea (34%), constipation (34%), and AST increased (31%), vomiting (30%), ALT increased (28%), and alopecia (27%).

Per the data cut off, 15 patients experienced Cycle 1 DLTs in Study C15010. Increased ALT or AST (or both) accounted for DLTs in 11 patients, febrile neutropenia was reported for 3 patients, and 1 patient experienced thrombocytopenia. In Arm 3, 1 event of febrile

neutropenia worsened from Grade 3 to Grade 5, and is listed twice in the table although it is one continuing event.

The MTD for Arm 1 was determined to be 25 mg/m^2 pevonedistat (dosing on Days 1, 3, and 5 with 75 mg/m^2 docetaxel dosing on Day 1 in a 21 day cycle). No MTD was determined for the Arm 2 Lead-in per protocol, but these DLTs informed the dose selection for paclitaxel and carboplatin in Arm 2: paclitaxel dose 175 mg/m^2 and a reduced dose for carboplatin of AUC5. The MTD for Arm 2 was determined to be 20 mg/m^2 pevonedistat (dosing on Days 1, 3, and 5 with 175 mg/m^2 paclitaxel and AUC5 carboplatin dosing on Day 1 in a 21 day cycle). The gemcitabine combination arm (Arm 3) was closed to enrollment due to lack of tolerability (MTD was not determined). A total of 26 (41%) patients experienced at least 1 SAE. Febrile neutropenia was the only event reported for at least 1 patient in each of the 4 treatment arms (reported for 2 of 26 patients in Arm 2 and 2 of 10 patients in Arm 3). Dyspnea was reported for 3 of the 22 patients in Arm 1 and for 1 patient in Arm 3. Abdominal pain was reported for 1 patient each in Arm 1 and Arm 3 and pneumonia was reported for 2 patients in Arm 1; all other events were reported for only 1 patient across the treatment arms. Eighteen patients discontinued the Study because of TEAEs. Events that resulted in study discontinuation that were assessed at least possibly related to study drug treatment included ALT and AST increased, blood bilirubin increased, and blood creatinine increased (1 patient each in Arm 1); platelet count decreased (1 patient in Arm 2), neuropathy peripheral (2 patients in Arm 2), neutropenia (1 patient in Arm 2); leukopenia, lymphopenia, and pneumonitis (1 patient each in Arm 3), and febrile neutropenia (2 patients in Arm 3). 6 on study deaths (within 30 days of the last dose of study drug) were reported with one death (Arm 3; due to febrile neutropenia) assessed as related to study treatment (pevonedistat and gemcitabine). 12 (22%) patients on Study C15010 had achieved PR or better. Two (9%) patients in Arm 2 achieved a CR; 3 (16%) patients in Arm 1, 1 (17%) patient in the Arm 2 Lead in, and 6 (26%) patients in Arm 2 achieved a PR.

1.3.3.2.3 Study C15011

In Part A of Study C15011, patients receive a single dose of pevonedistat given as an IV infusion on Day 1 and Day 8, and either concomitant oral fluconazole or itraconazole on Day 4 through Day 10. Patients are assessed for eligibility to continue in Part B (optional) after completion of Part A during a 2- to 8 week washout period. As of 22 January 2017, 36 of the 51 patients enrolled in Study C15011 have entered Part B of the study; these 36 patients have received a total of approximately 203 cycles of pevonedistat in combination with either docetaxel (n = 23; median 4 cycles; range 2-10) or the combination of

carboplatin and paclitaxel (n = 13; median 5 cycles; range 2-27). Overall, the most common AEs [occurring in ≥ 30% of patients (in Part A, or Part B)] were fatigue (45%, 53%) vomiting (45%, 50%), nausea (41%, 50%), decreased appetite (41%, 39%), dehydration (35%, 44%), constipation (33%, 39%), anemia (35%, 33%), stomatitis (Part B only 33%), diarrhea (31%, 39%), headache (Part B only 36%), and hypokalemia (Part B only 31%). A total of 30/51 (59%) patients experienced at least 1 SAE. Most SAEs were reported for 1 patient only; events reported for 2 or more patients included dyspnea, pneumonia and abdominal pain (3 patients each); deep vein thrombosis, hyperkalemia, and intestinal obstruction (2 patients each). Twelve (24%) patients experienced an SAE in Part A. Only one SAE (esophageal hemorrhage) in Part A occurred before the washout period and was not related to study treatment. Six patients experienced a total of 10 SAEs during Part B that were assessed as related to study treatment; these events included pneumonia (reported for 2 patients), failure to thrive, hypovolemic shock, respiratory failure, nausea, vomiting, chest discomfort, dyspnea, and septic shock. Seventeen patients discontinued participation in Study C15011 due to TEAE. Eighteen on study deaths (within 30 days of the last dose of study drug) have been reported; 1 of these deaths (due to respiratory failure) was assessed as related to study treatment (docetaxel). As of the cutoff date, 4 patients in Study C15011 who received pevonedistat in combination with docetaxel or carboplatin/paclitaxel achieved a PR in Part B of the study.

1.3.3.2.4 Pevonedistat-1012

The phase 1 Study Pevonedistat-1012 is an ongoing phase 1 study evaluating pevonedistat single agent or in combination with azacitidine in East Asian patients with AML or MDS. As of 22 January 2017, 10 patients had enrolled and 7 remain on study. The treatment arms are:

- Cohort S1: pevonedistat 25 mg/m^2 dosed on Days 1, 3, and 5 in a 21-day cycle.
- Cohort S2: pevonedistat 44 mg/m^2 dosed on Days 1, 3, and 5 in a 21-day cycle.
- Cohort C1: pevonedistat 10 mg/m^2 dosed on Days 1, 3, and 5 with azacitidine 75 mg/m^2 dosed on Days 1-5, 8-9 in a 28-day cycle.
- Cohort C2: pevonedistat 20 mg/m^2 dosed on Days 1, 3, and 5 with azacitidine 75 mg/m^2 dosed on Days 1-5, 8-9 in a 28-day cycle.

As of 22 January 2017, preliminary safety data are available for 10 patients enrolled who received therapy; these patients had completed a total of 27 treatment cycles, with median 2.0 cycles or 6.0 doses across the 4 treatment groups. The most common TEAEs (2 patients each) were fatigue, dizziness, and febrile neutropenia. Five (50%) patients reported an SAE during the study, with no event reported by more than 1 patient. Three patients discontinued treatment due to TEAE, none of which were considered treatment related. Three deaths occurred and were assessed as not related to the study treatment. Efficacy data were not available as of 22 January 2017.

1.3.3.2.5 Pevonedistat-2001

Pevonedistat-2001 is an ongoing, phase 2 study evaluating the efficacy and safety of pevonedistat+azacitidine versus single-agent azacitidine in patients (aged 18 years and older) with HR MDS, CMML, and low blast AML. Patients were enrolled in 1 of 2 treatment groups:

- Group 1: pevonedistat 20 mg/m^2 dosed on Days 1, 3, and 5 with azacitidine 75 mg/m^2 dosed on Days 1-5, 8-9 in a 28-day cycle.
- Group 2: single-agent azacitidine 75 mg/m^2 dosed on Days 1-5, 8-9 in a 28-day cycle.

As of 22 January 2017, 33 patients were treated with the combination of pevonedistat + azacitidine, and 34 patients received azacitidine alone. Collectively, the 33 patients in treatment Group 1 had received a total of 128 treatment cycles (median 10.0 doses). As of the cutoff date, preliminary data were available for 65 patients enrolled in the study. The most common TEAE reported was nausea (16 patients [25%]), followed by constipation (11 patients [17%]). Diarrhea, vomiting, cough, and neutropenia were reported by 10 (15%) patients each. Eighteen (28%) patients reported an SAE. The only SAEs experienced by more than 1 patient in either treatment group were febrile neutropenia (3 patients in the azacitidine treatment group and 1 patient in the pevonedistat + azacitidine treatment group) and pyrexia (2 patients in the pevonedistat + azacitidine treatment group). Two patients were discontinued from the study/study drug because of TEAEs; these events were not considered related to the study medication. No deaths occurred in the pevonedistat + azacitidine treatment group. Seven deaths occurred in the azacitidine treatment group; only febrile neutropenia was considered related to treatment. At data cutoff, 61 patients remained on the study; efficacy data were not available.

1.4 Potential Risks and Benefits

Although therapeutic efficacy is a desired outcome of treatment with pevonedistat, it is unknown whether patients will benefit from this study.

There are potential risks in the pevonedistat program that require monitoring. While these toxicities may be severe or life threatening, it is anticipated that they can be managed by clinical monitoring and intervention. Patients will be monitored for these potential toxicities and for unanticipated toxicities when they receive pevonedistat for at least 30 days after their last dose.

Because pevonedistat is considered a cytotoxic agent with limited human experience, patients considering future childbearing should consider autologous gamete cryopreservation prior to therapy with pevonedistat.

1.4.1 Common Side effects of Pevonedistat

Very Common (more than 1 in 10 people) side effects include:

- Myalgia, Arthralgia, Musculoskeletal pain
- Pyrexia
- Nausea
- Diarrhea
- Vomiting
- Alanine aminotransferase increased, Aspartate aminotransferase increased
- Tachycardia, and observations made on review of single agent vital sign data

1.4.2 Potential Risks of Pevonedistat from Phase 1 Studies

Events have been reported in completed phase 1 studies primarily at doses and schedules substantially higher than doses administered in current clinical studies. These events are being considered potential risks for the doses and schedules in the current studies, as follows:

- Multi-organ failure that could result in death.

- Renal failure.
    - The events of multi organ failure (hepatic, renal, and cardiac) with a fatal outcome, and renal failure alone, have been reported at doses of pevonedistat ranging from 110 to 278 mg/m^2.
- Cardiac arrhythmias.
    - All events were supraventricular arrhythmias; all except 1 were unrelated. The events of supraventricular arrhythmias were all considered as unrelated to pevonedistat except for 1 event of atrial fibrillation that occurred in a patient with a history of risk factors for cardiac disease.
- Myelosuppression with increased susceptibility to infection, bleeding, and anemia.
- Acute phase response.
- GI toxicity including or resulting in dehydration and/or electrolyte imbalance.
- Hypophosphatemia.

1.4.3 Potential Risks of Pevonedistat Confounded by Underlying Disease or Malignancy

Events have been reported from clinical trials that are confounded by the patient's underlying medical condition, including malignancy. These events are noted in the absence of randomized, controlled data:

- Fatigue.
- Chills.
- Decreased appetite.
- Neutropenia.
- Febrile neutropenia.
- GI bleeding.

- All events were assessed by the investigator as unrelated; the majority occurred in the setting of thrombocytopenia.

- Multi-organ failure in the setting of infection.

1.4.4 Potential Risks of Pevonedistat Primarily Based on Findings from Animal Studies

Potential risks that are derived from findings in animal studies in rats and dogs include:

- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.
- Cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure, and increased diastolic blood pressure.
- Enteropathy (including dehydration and electrolyte loss) with secondary sepsis.
- Effects on the testes and ovaries that represent a reproductive hazard including sterility.
- Increased developmental risk to the 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 aPTT.
- Local tissue injury when administered SC.

It is possible that pevonedistat will have toxicities that were not observed in or predicted from the studies completed in rats and dogs, or have not yet been identified in patients, which may be severe or fatal.

For detailed information please consult the current IB.

1.4.5 Potential Risks and Benefits of Azacitidine

Azacitidine (VIDAZA) is a nucleoside analogue of the pyrimidine cytidine, and is approved by the United States Food and Drug Administration (FDA) for the following 5 subtypes of the French-American-British (FAB) classification system of MDS: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and CMML[32].

As listed in the current product insert[32], the most common adverse reactions (>30%) associated with azacitidine by the subcutaneous (SC) or IV routes are:

- Nausea
- Cytopenias, including anemia, thrombocytopenia, leukopenia, and neutropenia
- Vomiting
- Pyrexia
- Diarrhea
- Injection site erythema
- Constipation
- Ecchymosis
- Petechiae (IV route only)
- Rigors (IV route only)
- Weakness (IV route only)
- Hypokalemia (IV route only).

Azacitidine adverse reactions most frequently (>2%) resulting in clinical intervention (SC or IV Route) are:

- Discontinuation: leukopenia, thrombocytopenia, neutropenia.

- Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.
- Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

1.4.6 Potential Risks of Combination Therapy with Pevonedistat and Azacitidine

Pevonedistat (10-30 mg/m^2 administered on Days 1, 3, and 5 in a 28) in combination with azacitidine (75 mg/m^2 administered on Days 1-5 and 8-9 in a 28-day cycle) has been studied in three ongoing clinical studies in MDS, CMML and/or AML patients (See Study C15009, Pevonedistat-1012, and Pevonedistat-2001 in Section 1.3.3.2).

The most common adverse reactions experienced by at least 2 patients and reported by ≥ 25% of patients treated with the pevonedistat/azacitidine combination on any one of these studies include:

- Constipation
- Nausea
- Fatigue
- Anemia
- Febrile neutropenia
- Decreased appetite
- Thrombocytopenia or decrease in platelets.
- Fever

Other adverse reactions reported by at least 2 patients and between 10% and 25% of patients treated with the pevonedistat/azacitidine combination in any one of these studies:

- Vomiting
- Diarrhea
- Cough

- Insomnia
- Neutropenia or decrease in neutrophil count
- Pneumonia
- Increased liver function tests (AST, ALT, or ALP)
- Blood creatinine increased
- Peripheral edema
- Dyspnea
- Hyponatremia
- Hypotension
- Limb pain
- Weight loss
- Abdominal pain
- Chills
- Fall
- Headache
- Hypokalemia
- Leukopenia
- Oropharyngeal pain.
- Dizziness

Myelosuppression with increased susceptibility to infection, bleeding, and anemia are considered potential risks of pevonedistat because of the occurrence of these events in phase

1 clinical studies at high doses; decreased appetite and febrile neutropenia are considered potential risks confounded by underlying disease or malignancy.

As of 22 January 2017, in the combination pevonedistat/azacitidine treatment groups of Study C15009, Pevonedistat-1012 or Pevonedistat-2001, respectively 17, 1, and 0 deaths within 30 days of the last dose of study drug had been reported; none of the deaths was assessed as related to study treatment.

1.5 Additional Safety Considerations

1.5.1 Cycle 1, Day 1 Toxicity/Multi Organ Failure

A comprehensive review of the clinical trial safety data has shown that C1D1 toxicity involving multi-organ failure, including SAEs of renal, hepatic, and cardiac failure, some with a fatal outcome, has been observed in phase 1, single agent pevonedistat studies at doses equal to or above 110 mg/m^2. Based on the observation that these events are associated with higher pevonedistat doses, Millennium Pharmaceuticals, Inc. determined that all newly enrolling patients would receive pevonedistat at doses equal to or below 100 mg/m^2.

The current understanding of the renal toxicity observed with pevonedistat suggests that it is not a primary event but is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response.

Nonclinical investigative activities were undertaken to better understand the potential physiology behind the C1D1 events observed with pevonedistat dosing. As summarized in the latest IB, a model in which a minimally toxic, single dose of pevonedistat was administered with TNFα had several hallmarks associated with septic and/or cytokine-induced shock. The overall time course and target organs affected in this nonclinical model also appeared to closely mimic those observed in clinical C1D1 events at single agent doses ranging from 110 to 278 mg/m^2.

In October 2012, a revised risk mitigation strategy limiting the dose to no higher than 50 mg/m^2 for dosing on Days 1, 3, and 5 and no higher than 100 mg/m^2 for dosing on Days 1, 4, 8, and 11 or 1, 8, and 15 for all studies for ssingle agent administration was implemented across the pevonedistat program. As of January 2017, approximately 240 additional patients have been treated in single agent and combination studies, and no C1D1 SAEs as described above have been observed. These patients received pevonedistat at a dose of 50 to 100

mg/m^2 as a single agent, a dose of 15 to 30 mg/m^2 in combination with different standard of care therapies, or a dose of 8 mg/m^2 in combination with a CYP3A inhibitor.

The Days 1, 3, and 5 schedule for pevonedistat infusion was chosen for further studies. The MTD for that schedule for patients with AML in Study C15003 was determined to be 59 mg/m2, and the MTD for patients with solid tumors in Study C15001 was determined to be 67 mg/m2.

1.5.2 Guidance for Clinical Assessment and Management of Hemodynamic Compromise

Due to the underlying conditions of patients with advanced malignancies, patients must be carefully evaluated at screening and before each pevonedistat dose for early symptoms and signs of hemodynamic compromise and active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. For those 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. For all patients with anemia, and especially for patients 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 patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines. Patients who experience signs and symptoms of hemodynamic compromise after pevonedistat dosing (eg, tachycardia, hypotension, orthostasis, and changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care, including hospitalization as clinically indicated.

1.5.3 Guidance for Management of Patients with Blood Cell Counts Greater than 50,000/µL

One patient died of AML complicated by leukostasis within hours after receiving the first dose of pevonedistat. This patient experienced rapidly increasing blast counts (to levels greater than 100,000/µL) before receiving the first dose of pevonedistat on C1D1. This patient was not treated with hydroxyurea before receiving treatment with pevonedistat. Patients with AML who experience extremely high leukemic blast cell count are at high risk of leukostasis, an AML complication characterized by an extremely elevated blast cell count causing symptoms of decreased tissue perfusion. To mitigate the risk of leukostasis, Study

C15003 was amended to require that patients have a WBC count ≤ 50,000/µL at screening and before pevonedistat dosing during the first cycle of treatment.

In response to this event, AML clinical study protocols were updated to include a monitoring and treatment plan for leukocytosis and an exclusion criterion requiring a WBC count below 50,000/µL at screening and on pevonedistat dosing days in Cycle 1. For patients who develop symptoms of leukostasis while on the study, pevonedistat treatment should be withheld until the leukostasis symptoms are controlled. Treatment of leukostasis symptoms may include leukapheresis and hydroxyurea administration per study site institutional guidelines. When the WBC count of the patient is < 50,000/µL and symptoms are improved, pevonedistat treatment may be restarted after consulting with the project clinician.

1.5.4 **Increases in Serum Creatinine**

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

1.5.5 **Increases in Liver Enzymes and Biochemical Tests**

Grade 1 to Grade 4 increases in adverse events related to liver function analyses (such as for liver transaminases [up to Grade 4], bilirubin [up to Grade 3], and alkaline phosphatase [up to Grade 3]), have been noted following administration of pevonedistat in patients with advanced malignancies receiving pevonedistat as a single agent and in combination with standard of care cytotoxic therapies. Among the single-agent studies, one patient in Study C15001 with metastatic colon cancer experienced a Grade 4 adverse event related to liver function analyses (alanine aminotransferase increased). In Study C15009, in patients with AML treated with pevonedistat in combination with azacitidine, Grade 4 increases for adverse events related to liver function analyses occurred in 2 patients as DLTs (alanine aminotransferase increased, aspartate aminotransferase increased). A third patient in Study C15009 experienced a Grade 4 adverse event (aspartate aminotransferase increased) that was not assessed as a DLT. In Study C15010 in patients with solid tumors treated with pevonedistat in combination with docetaxel, gemcitabine, or carboplatin plus paclitaxel, and also in Study C15011, a drug-drug interaction study, adverse events related to liver function analyses up to Grade 3 were observed.

All patients experiencing these increases in laboratory values have been asymptomatic. The elevations in laboratory values have been reversible with dose modification including dose delay and reduction.

1.5.6 Drug Drug Interactions (DDIs)

Because the metabolic and excretion pathways of pevonedistat remain to be characterized in humans, the risk of DDIs between pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data. On the basis of preliminary findings, administration of pevonedistat with moderate and strong CYP3A inhibitors and P-gp inhibitors is permitted, while use of clinically significant CYP3A inducers should be avoided. On the basis of in vitro transport studies, and until further investigation is performed, coadministration with BCRP inhibitors should not be allowed in clinical studies of pevonedistat.

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.

1.6 Study Rationale

DNA methyl-transferase inhibitors—either 5'azacitidine or decitabine given for 7 or 5 consecutive days, respectively, every 28-42 days—comprise the standard of care therapy for MDS patients requiring disease modifying therapy[7,33,34]. Although azacitidine has typically been administered over 7 consecutive days, a recent study of alternative dosing regimens reported that dosing azacitidine over 5 consecutive days was better tolerated and demonstrated equivalent, if not improved, outcomes[35]. Regardless of the regimen, response rates are modest with only about half of patients achieving an objective response, with complete remission in <25% of patients.

In addition to the modest success of DNMTi therapy, the majority of patients who do respond initially will relapse within 2 years[36,37]. After failure of DNMTi therapy there are limited treatment options and survival is poor—estimated to be between 4-19 months, with patients fit for hematopoietic stem cell transplant surviving longest. In a meta-analysis of 435 MDS patients with intermediate-2 (INT-2) or High risk IPSS scores, median survival

was only 5.6 months after failure of azacitidine[35]. In a smaller, single-institution study of 89 MDS patients who failed decitabine, medican survival was 4.3 months[36]

While the treatment of MDS is limited both in the number of effective therapies and in the magnitude of success of those available therapies, the optimal treatment of MDS/MPN is even more poorly defined. Both the rarity and heterogeneity of MDS/MPNs have hindered development of therapies for many years. CMML are often treated with DNMTi, but relapsed CMML patients and other MDS/MPN patients have few options[37]. As mechanistic understanding of myeloid diseases continues to grow, there is a renewed interest to include MDS/MPN in the investigation of new targeted agents being tested in MDS or MPN. Likewise, the recent development of clinical trial response criteria in MDS/MPN provides a platform to objectively assess response in these diseases[38].

Single-agent pevonedistat activity in myeloid malignancies was confirmed in a phase I trial for relapsed/refractory AML patients[27] Furthermore, pevonedistat and azacitidine combination therapy has demonstrated encouraging results in a recent phase I study C15009 (see Section 1.3.3.2.1). In 64 evaluable elderly patients with AML treated with pevonedistat and azacitidine, 60% achieved partial remission (PR) or better, with 19 complete remissions and 5 complete remissions with incomplete hematologic recovery, indicating significant additive anti-leukemic effect of pevonedistat to DNMTi. The results of study C15009 raised the hypothesis that MDS and MDS/MPN patients, in particular those with increased blasts (e.g. RAEB1/RAEB2), could derive benefit from pevonedistat in combination with azacitidine. This hypothesis forms the basis of the current study to evaluate the combination of pevonedistat and azacitidine in the setting of DNMTi failure in patients with relapsed/refractory MDS or MDS/MPN.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To compare survival of patients treated with a combination of pevonedistat and azacitidine after failure of DNMTi to historical survival for patients with relapsed/refractory MDS or MDS/MPN who are ineligible for hematopoietic stem cell transplant (HSCT)

2.2 Secondary Objectives

- To determine the rate of hematologic improvement (HI) in patients with relapsed/refractory MDS or MDS/MPN treated with pevonedistat and azacitidine after DNMTi failure

- To determine the CR and marrow CR rates in patients with relapsed/refractory MDS or MDS/MPN treated with pevonedistat and azacitidine after DNMTi failure

- To determine the reduction of bone marrow blasts in patients with relapsed/refractory MDS or MDS/MPN treated with pevonedistat and azacitidine after DNMTi failure

2.3 Tertiary/Exploratory Objectives

- To correlate the mutation burden in patients with relapsed/refractory MDS or MDS/MPN with response to treatment with pevonedistat and azacitidine

- To correlate genomic aberrations with rate of response and survival in relapsed/refractory MDS or MDS/MPN patients treated with pevonedistat and azacitidine

- To measure the effect of pevonedistat treatment in combination with azacitidine on quality of life in patients with relapsed/refractory MDS or MDS/MPN

- To define epigenetic biomarkers for pevonedistat use in relapsed/refractory MDS or MDS/MPN

3. STUDY ENDPOINTS

3.1 Primary Endpoints

- Overall survival time

- 1-year overall survival rate

3.2 Secondary Endpoints

- Hematologic parameters will be assessed on days 1, 3 and 5 of each cycle of protocol-indicated treatment, at the end of treatment and in follow-up. Hematologic parameters include:

- Complete and differential blood counts (peripheral blood)
- Transfusion requirements.

- Bone marrow biopsy and aspirate will be assessed on Cycle 3, Day 1 and Cycle 7, Day 1, and at the End of Treatment and/or at the time of suspected Disease Progression. Bone marrow measurements include:
  - Morphologic features (e.g. presence of dysplastic features)
  - Presence of cytogenetic and/or molecular aberrancies
  - Myeloblast count.

3.3 Tertiary/Exploratory Endpoints

- Number and allele frequency of specific molecular mutations in a panel of 37 genes frequently mutated in myeloid malignancies will be determined by next generation sequencing before and after protocol-directed therapy. Results will be correlated with response. Clonal evolution and the relationship between response rates and mutations will be explored.

- Changes in gene expression in bone-marrow derived hematopoietic cells,isolated before and after treatment with pevonedistat and azacitidine, will be identified using RNAseq and ProSeq expression analyses: RNAseq will reveal coincident gene expression changes; whereas ProSeq will examine true transcription-related changes by measuring RNA polymerase activity throughout the genome. Differentially expressed genes of interest identified by these analyses are intended for further interrogation. Mass cytometry may be used to assess changes in protein expression of differentially expressed genes of interest.

- Patient symptoms and quality of life will be assessed at screening, on Day 1 of each cycle, at the End of Treatment (EOT) and at the Follow-Up visit using the FACT-Leu Questionnaire available through http://www.facit.org) for MDS patients or the MPN-SAF TSS for MDS/MPN patients.

- Pevonedistat-induced changes in genome methylation will be assessed by whole genome methylation studies (WGMS) conducted on bone marrow-derived CD34+ cells. Given the clinically apparent synergy between azacitidine and pevonedistat

treatment in AML, we hypothesize that pevonedistat may be amplifying the hypomethylating signal of azacitidine. We will perform WGMS using DNA isolated from bone marrow-derived cells from two subsets of patients identified as either poor or good responders to PevAz.

4. STUDY DESIGN

4.1 Overview of Study Design

4.1.1 Study Overview by Visit

4.1.1.1 Screening Assessments

Prior to performing any study-directed procedures, patient informed consent must be obtained.

The following procedures must be completed ≤ 28 days prior to a patient's first dose of protocol-indicated treatment

- Prior to initiating treatment, all patients must have morphologically confirmed diagnosis of MDS or MDS/MPN. After informed consent, an expanded screening window of up to 28 days prior to Cycle 1, Day 1 is applicable for any necessary disease-specific testing (i.e. if results not already available). A patient without documentation from an acceptable local or designated lab of eligible MDS or MDS/MPN status will not be eligible to enroll in the study.

The following procedures must be completed ≤ 21 days prior to a patient's first dose of protocol-indicated treatment:

- Medical history and demographics.
- Comprehensive physical exam conducted by a physician or qualified designee (e.g. nurse practitioner).
- Eastern Cooperative Oncology Group (ECOG) Performance Status.
- Height.
- Weight.

- Concomitant medication (taken up to 14 days prior to signing informed consent) and adverse event review.

- Quality of life questionnaire (either FACT-Leu or MPN-SAF).

- Complete blood count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).

- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.

- Coagulation including aPTT and PT

- Serum Pregnancy test in women of childbearing potential (as defined in the SCHEDULE OF EVENTS and Section 4.1.2.11).

- 12-lead ECG (single on local equipment)

- In addition to bone marrow tissue (archival or fresh) necessary for baseline MDS or MDS/MPN eligibility analysis, additional FRESH bone marrow biopsy and aspirate is also REQUIRED at baseline for exploratory research (see SCHEDULE OF EVENTS and Section 4.1.2.13 for additional detail). Requirement for bone marrow biopsy may be waived with approval of the study chair in the event that a bone marrow biopsy cannot be obtained.

  Tissue shall be considered "fresh" when it is obtained from a procedure performed at the study site no more than 28 days before initiating treatment on Cycle 1, Day 1.

  Patients who consent to undergo fresh bone marrow biopsy and aspirate prior to initiating study treatment, but whose disease is deemed inaccessible (or insufficient) to a reasonably safe marrow biopsy and aspirate, may still be allowed to enroll upon discussion with and approval by the study chair (if otherwise eligible and with known MDS or MDS/MPN status).

  Prior to initiating treatment, a patient's screening team must have documentation that fresh bone marrow biopsy and aspirate has been performed and reasonable attempt made to obtain biospecimens for exploratory research. (Provided that the diagnosis

of MDS or MDS/MPN is not in question, waiting for histological analysis or confirmation that acquired specimens are known to contain tissue sufficient for exploratory analysis, is not a requirement prior to initiating study treatment.)

- Pharmacogenetic (PG) and pharmacodynamic (PhD) blood samples should be obtained prior to the baseline bone marrow biopsy/aspirate procedure.

4.1.1.2 Cycle 1, Day 1 Assessments

On Cycle 1, Day 1, Hematology and Blood Chemistry and Serum Pregnancy Test performed for eligibility screening more than 3 calendar days prior to Cycle 1, Day 1 must be repeated to confirm adequate organ function prior to initiating treatment. The following assessments and procedures must be completed on Cycle 1, Day 1, unless previously completed ≤ 3 calendar days prior to a patient's first dose of protocol-indicated treatment (i.e. if Cycle 1 Day 1 falls on a Monday, assessments made and procedures performed on the preceding Friday, Saturday or Sunday need not be repeated, but may be performed at investigator discretion):

- Targeted physical exam by a physician , including assessment of the lungs, heart, abdomen and any other body area deemed appropriate by the treating physician or qualified designee; or comprehensive physical exam if clinically indicated. For MDS/MPN patients only, physical examination should include assessment for presence of palpable hepatosplenomegaly indicative of extramedullary hematopoiesis.

- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).

- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.

- Weight

- Serum pregnancy test should be performed for WOCBP only (as defined in Section 4.1.2.11).

On Cycle 1, Day 1, the following procedures will be completed:

- ECOG performance status.
- Concomitant medication and adverse event review.
- Quality of life questionnaire.
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).
- 12-lead ECG (single on local equipment) will be obtained after study treatment is administered

4.1.1.3 Cycle 1, Day 2 Procedures

- Azacitidine injection or infusion.

4.1.1.4 Cycle 1, Day 3 Assessments and Procedures

- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).

4.1.1.5 Cycle 1, Day 4 Procedures

- Azacitidine injection or infusion.

4.1.1.6 Cycle 1, Day 5 Assessments and Procedures

- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP,

calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.

- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).
- 12-lead ECG (single on local equipment) will be obtained after study treatment is administered

4.1.1.7 Cycle 1, Day 15 Assessments

- Targeted physical exam by physician or qualified designee (e.g. nurse practitioner), including assessment of the lungs, heart, abdomen and any other body area deemed appropriate by the treating physician or qualified designee; or comprehensive physical exam if clinically indicated.
- Vital signs
- Adverse event surveillance.
- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.

4.1.1.8 Additional Cycles, Day 1 Assessments and Procedures

In the absence of delayed dosing (e.g. due to an adverse event), every reasonable effort should be made to remain on a consistent schedule of 4 Week (28-day) cycles; but for purpose of accommodating holidays, scheduling limitations, etc, subsequent cycles (i.e. Cycles ≥ 2) may occur up to every 28 ± 3 days.

For patients that continue beyond Cycle 1, the following assessments will occur on Day 1 of each new cycle:

- Targeted physical exam by physician or qualified designee (e.g. nurse practitioner), including assessment of the lungs, heart, abdomen and any other body area deemed appropriate by the treating physician or qualified designee; or comprehensive physical exam if clinically indicated.
    - For Day 1 of cycles 3 and 7, physical examination of MDS/MPN patients should include assessment for presence of palpable hepatosplenomegaly, indicative of extramedullary hematopoiesis.
- ECOG Performance Status.
- Weight.
- Concomitant medication and adverse event review.
- Quality of life questionnaire.
- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.
- Serum or urine pregnancy test should be performed on Day 1 of each subsequent cycle for WOCBP (as defined in Section 4.1.2.110).
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).

On Day 1 of Cycle 2 only, the following assessments and procedure will be completed:

- Coagulation including aPTT and PT
- 12-lead ECG (single on local equipment) will be obtained after study treatment is administered

On Day 1 of Cycles 3 and 7, the following procedures will be completed:

- Fresh bone marrow biopsy and aspirate required prior to treatment on Cycle 3, Day 1 and Cycle 7, Day 1 (acceptable window up to 7 days prior to c3d1 & c7d1 treatment).

- Pre-dose PG and PhD blood samples: obtain on c3d1 and c7d1 at a single time point – i.e. prior to scheduled bone marrow procedure / scheduled azacitidine treatment.

4.1.1.9 Additional Cycles, Day 2 Procedures

- Azacitidine injection or infusion.

4.1.1.10 Additional Cycles, Day 3 Assessments and Procedures

- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).

- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.

- Azacitidine injection or infusion.

- Pevonedistat infusion (AFTER completion of azacitidine).

Note: If pevonedistat and azacitidine treatment continues beyond 12 cycles, due to continued objective response and/or clinical benefit, the frequency of CBC and Blood Chemistry will be at the discretion of the treating investigator in subsequent cycles (i.e. in cycles ≥13).

4.1.1.11 Additional Cycles, Day 4 Procedures

- Azacitidine injection or infusion.

4.1.1.12 Additional Cycles, Day 5 Assessments and Procedures

- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).

- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP,

calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.

- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).

On Day 5 of Cycle2 only, the following procedure will be completed:

- 12-lead ECG (single on local equipment) will be obtained after study treatment is administered

Note: If pevonedistat and azacitidine treatment continues beyond 12 cycles, due to continued objective response and/or clinical benefit, the frequency of CBC and blood chemistry will be at the discretion of the treating investigator in subsequent cycles (i.e. in cycles ≥13).

4.1.1.13 End-of-Treatment / Withdrawal Assessments and Procedures

Reasonable effort should be made to complete EOT/Withdrawal procedures on the day it is decided that a patient will no longer receive protocol-indicated treatment.

The EOT procedures must be completed subsequent to and not later than 14 days after investigator decision to permanently discontinue protocol treatment with azacitidine/pevonedistat (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy.

- Comprehensive physical exam conducted by a physician; or a targeted physical exam (including assessment of the lungs, abdomen and any other body area deemed appropriate) by the conducting physician or qualified designee (e.g. nurse practitioner). If a targeted physical exam is done at EOT, then a comprehensive physical exam must be performed by a physician at the 30-Day Follow-Up Visit. For MDS/MPN patients, physical examination should include assessment for presence of palpable hepatosplenomegaly, indicative of extramedullary hematopoiesis.
- ECOG Performance Status.
- Weight.

- Concomitant medication and adverse event review.
- Quality of life questionnaire.
- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.
- Serum or urine pregnancy test in women of childbearing potential (as defined in Section 04.1.2.11).
- 12 lead ECG (single on local equipment).
- Fresh bone marrow biopsy and aspirate required at End-of-Treatment, or at time of suspected Progressive Disease. If a patient discontinues study treatment for reason other than progressive disease confirmed by marrow procedure (e.g. due to adverse event), then every effort should be made to obtain fresh bone marrow biopsy and aspirate samples to evaluate response and to obtain biospecimens for exploratory research. If progressive disease is suspected between scheduled study bone marrow examinations (e.g. due to suspicious peripheral blood counts), fresh bone marrow biopsy and aspirate samples must be collected in a subsequent procedure to evaluate for progressive disease and to obtain bone marrow aspirate for research purposes. If progressive disease is confirmed in that procedure and the patient will terminate the study as a result, it can be considered synonymous with their End of Treatment evaluation.
- PG and PhD blood samples. Note: If a bone marrow examination is performed for suspected disease progression, then the PG/PhD blood samples should be obtained on the same-day prior to the bone marrow procedure.

Also, for patients who discontinue study treatment for reason other than progressive disease confirmed by marrow procedure (e.g. suspicious peripheral blood counts), please note the study may continue to request results of laboratory data conducted outside of the study but

related to bone marrow exams and peripheral blood counts, until progressive disease is ultimately confirmed by marrow procedure.

4.1.1.14 30-Day Follow-Up Visit Assessments

Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities. (Note it is possible that EOT and Follow-Up visit items might both be completed in as few as a single clinic visit.)

A Follow-up clinic visit is to be completed 30 days (+14 days) after patient's final treatment with azacitidine or pevonedistat (whichever occurs last), in order to undergo the following assessments:

- Comprehensive physical exam conducted by a physician – if comprehensive exam was not already conducted by a physician at the EOT visit; otherwise a targeted physical exam (including assessment of the lungs, heart, abdomen and any other body area deemed appropriate) conducted by a physician or other qualified designee (e.g. nurse practitioner).
- ECOG Performance Status.
- Weight.
- Concomitant medication and adverse event review.
- Quality of life questionnaire.
- CBC with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood chemistry including sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein.

4.1.1.15 Survival Follow-Up

Each patient will be followed for survival every 3 months (± 14 days) after patient's final treatment with azacitidine or pevonedistat (whichever occurs last) until death, end of the study, until patient withdraws consent, or for a maximum of 4 years after a patient's final treatment with pevonedistat/azacitidine – whichever comes first. Survival contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

4.1.2 Study Overview by Procedure

4.1.2.1 Screening

Assessments performed as standard-of-care within the screening window may be used for screening. Baseline characteristics to be evaluated during screening include but are not limited to: demographics, medical and surgical history, extent of disease burden and morphology, prior anti-cancer treatment, and documentation of MDS or MDS/MPN status as resulted from an acceptable local or designated lab.

4.1.2.2 Informed Consent

Informed consent must be obtained before any study-specific screening assessments are performed. Screening assessments are to be performed within 14 days prior to Day 1 of Cycle 1 unless otherwise noted (e.g. see immediately below paragraph, regarding disease-specific testing).

4.1.2.3 MDS or MDS/MPN Diagnosis

Prior to initiating treatment, all patients must have morphologically confirmed diagnosis of MDS or MDS/MPN. After informed consent, an expanded screening window of up to 28 days prior to Cycle 1, Day 1 is applicable for any necessary disease-specific testing (i.e. if MDS or MDS/MPN diagnosis has not already been established). A patient without documentation from an acceptable local or designated lab of eligible MDS or MDS/MPN status will not be eligible to enroll in the study.

4.1.2.4 Physical Examination

A comprehensive physical exam will be done at screening; and at the End-of-Treatment or 30-day Follow-Up visit.

At other visits indicated in Section 4.1.1, a targeted physical examination may be done including assessment of the lungs, heart, abdomen and any other body area deemed appropriate by the treating physician or qualified designee (e.g. nurse practitioner), unless the patient's study physician considers a comprehensive physical examination necessary.

For cycles 1, 3, 7 Day 1 visits and the EOT visit, physical examination of MDS/MPN patients should include assessment for palpable hepatosplenomegaly, indicative of extramedullary hematopoiesis.

Cycle 1, Day 1 and either EOT or Follow-Up exams must be done by a physician; at other time points, physical exams may be conducted by either a physician or other qualified designee (e.g. nurse practitioner).

4.1.2.5 Height and Weight

Height must be measured only during screening. Weight must be measured at screening; on Day 1 of each cycle; and at EOT and Follow-up visits.

Note: each dose of azacitidine and pevonedistat must be adjusted if patient's body weight changes > ±10%.

4.1.2.6 Review of Concomitant Medications and Adverse Events

Review and capture of all concomitant medications will be performed at each visit as indicated in the SCHEDULE OF EVENTS. Concomitant medications are defined as any prescription medications or over-the-counter preparations used by a patient within 14 days before signing informed consent and continuing through the 30-day Follow-Up study visit. After signing the informed consent, adverse events will be collected as detailed in protocol Section 8. All adverse events will be recorded until 30 days after a patient's last azacitidine or pevonedistat treatment (whichever occurs last) or until initiation of another anti-cancer therapy – whichever occurs first.

4.1.2.7 Quality of Life Questionnaire.

Patient symptoms and quality of life will be assessed at screening, on Day 1 of each cycle, at the End of Treatment, and at the Follow-Up visit using the FACT-Leu Questionnaire available through http://www.facit.org for MDS patients or the MPN-SAF TSS for MDS/MPN patients.

4.1.2.8 CBC with Differential

Hematology results to include white blood cell count with differential, hemoglobin, hematocrit, and platelet count will be assessed locally at screening; on Days 1, 3 and 5 of Cycles 1-12; at EOT and at the Follow-Up visit.

If disease progression or hematologic toxicity is suspected or confirmed, frequency may be increased as clinically indicated to include additional evaluations between scheduled assessments.

On days of pevonedistat infusion (i.e. Days 1, 3 and 5) of cycles 1-12 laboratory results must be available and assessed prior to azacitidine or pevonedistat treatment. If treatment continues beyond 12 cycles, due to continued objective response and/or clinical benefit, then frequency of laboratory studies will be at the discretion of the treating investigator in subsequent cycles (i.e. in cycles ≥13).

4.1.2.9 Blood Chemistry

Blood chemistry (to include sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, calcium, magnesium, phosphate (phosphorus), albumin, uric acid (urate) and total protein) will be assessed locally at screening; on Days 1, 3 and 5 of Cycles 1-12; at EOT and at the Follow-Up visit.

Frequency of blood chemistry assessment may be increased to include additional evaluations between scheduled assessments as clinically indicated for suspected or confirmed adverse events.

On days of pevonedistat infusion (i.e. Days 1, 3 and 5) of cycles 1-12 laboratory results must be available and assessed prior to azacitidine or pevonedistat treatment. If treatment continues beyond 12 cycles, due to continued objective response and/or clinical benefit, then frequency of laboratory studies will be at the discretion of the treating investigator in subsequent cycles (i.e. in cycles ≥13).

4.1.2.10 Coagulation Panel

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) will be measured during screening, on Cycle 2 Day 1, and as clinically warranted once study treatment has been initiated.

4.1.2.11 Pregnancy Test

Serum pregnancy test for women of childbearing potential (WOCBP) required during screening. Serum or urine pregnancy test must be performed on Day 1 of each cycle and at the EOT for WOCBP.

WOCBP are defined as those not surgically sterile or not post-menopausal (i.e. if a female patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for 12 months in the absence of an alternative medical cause, then patient will be considered a WOCBP).

Postmenopausal status in females under 55 years of age should be confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women (if a patient's postmenopausal status is considered for childbearing potential and study-required contraception).

4.1.2.12 Electrocardiogram

One standard 12-lead ECG using local site equipment will be performed during Screening and at the EOT visit. During study treatment, one standard 12-lead ECG will be performed using local site equipment on Day 1 and 5 of Cycles 1 and 2, and should be performed following administration of azacitidine and pevonedistat on treatment days. Additional ECGs as clinically indicated.

4.1.2.13 Pre-Treatment Bone Marrow Biopsy and Aspirate for Exploratory Research

In addition to bone marrow tissue necessary for baseline MDS or MDS/MPN eligibility analysis, additional fresh bone marrow biopsy and aspirate is also REQUIRED at baseline for exploratory research (i.e. obtained from a procedure performed after informed consent is signed and no more than 28 days prior to initiating treatment on Cycle 1, Day 1). Requirement for bone marrow biopsy may be waived with approval of the study chair in the event that a bone marrow biopsy cannot be obtained.

If the patient does consent to a fresh procedure, but the patient's disease is deemed inaccessible (or insufficient) to a reasonably safe marrow biopsy and aspirate, then the patient may be allowed to enroll upon discussion with and approval by the study chair (if otherwise eligible and with known MDS or MDS/MPN status).

Prior to initiating treatment, a patient's screening team must have documentation that fresh bone marrow biopsy and aspirate has been performed and reasonable attempt made to obtain

biospecimens for exploratory research. Waiting for histological analysis or confirmation that acquired specimens are known to contain tissue sufficient for exploratory analysis, is not a requirement prior to initiating study treatment. Note: If a patient has a fresh biopsy/aspirate procedure done for baseline MDS or MDS/MPN eligibility testing, a second fresh procedure is not required if consent was obtained and biospecimens for exploratory research were collected at the time of the initial bone marrow examination.

4.1.2.14 Fresh Bone Marrow Biopsy and Aspirate (on-study and at progression)

In addition to baseline evaluation, fresh bone marrow biopsy and aspirate will be performed prior to treatment on Cycle 3, Day 1 and Cycle 7, Day 1 (acceptable windows up to 7 days prior to c3d1 & c7d1 treatment); and at End-of-Treatment (≤ 14 days after last study treatment) or time of suspected Progressive Disease. Tissue is to be collected both for assessment of disease response, as well as for correlative research.

If a patient discontinues study treatment for reason other than progressive disease confirmed by marrow procedure (e.g. due to adverse event), then every effort should be made to obtain fresh bone marrow biopsy and aspirate samples to evaluate response and to obtain biospecimens for exploratory research. If progressive disease is suspected between scheduled study bone marrow examinations (e.g. due to suspicious peripheral blood counts), fresh bone marrow biopsy and aspirate samples should be collected in a subsequent procedure to evaluate for progressive disease and to obtain bone marrow aspirate for research purposes. If progressive disease is confirmed in that procedure and the patient will terminate the study as a result, it can be considered synonymous with their end of treatment evaluation.

Also, at any time during the study, if additional bone marrow biopsy/aspirates are performed as standard-of-care, then a sample of the marrow aspirate, if available, may be requested for research purposes.

4.1.2.15 Pharmacogenetic (PG) and Pharmacodynamic (PhD) Blood Samples

Pharmacogenetic and Pharmacodynamic blood samples for research are to be obtained coincident with scheduled study bone marrow biopsy and aspirate at Baseline (i.e. on same-day prior to the fresh baseline bone marrow biopsy and aspirate); Pre-Dose prior to scheduled azacitidine treatment: on Day 1 of Cycles 3 and 7; and at the End-of-Treatment visit.

(Note: on Day 1 of Cycles 3 and 7, these samples should be obtained at a single time point PRIOR to scheduled bone marrow procedure / prior to scheduled azacitidine treatment and ideally coincident with blood obtained for hematology and blood chemistry evaluation.)

If disease progression is suspected and bone marrow biopsy is performed or if bone marrow biopsy and aspirate are conducted after EOT (e.g. not previously obtained at the EOT visit, because patient discontinued study treatment for reason other than progression confirmed by marrow biopsy) or if additional bone marrow biopsy and aspirate are performed standard of care at any time while on study, then an additional PG/PhD blood sample should be obtained on the same-day as the progression procedure.

4.1.2.16 Survival Follow-Up

Each patient will be followed for survival every 3 months (± 14 days) after patient's final treatment with azacitidine or pevonedistat (whichever occurs last) until death, end of the study, until patient withdraws consent, or for a maximum of 4 years after a patient's final treatment with azacitidine/pevonedistat – whichever comes first.

Survival contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

4.1.2.17 Handling of Biological Samples

All biological samples analyzed locally will be collected and handled according to local institutional practices.

All biological samples to be analyzed centrally will be collected and handled according to a detailed laboratory manual. All central samples are scheduled for storage at the Savona Laboratory in Nashville in liquid nitrogen. As an overview, peripheral blood and bone marrow aspirate samples will be obtained for isolation of DNA and RNA intended to be used for mutational analysis and gene expression studies; for protein isolation intended for protein expression studies; and for whole cell analyses, such as mass cytometry.

4.1.2.18 Specimen Banking

Retention time for biologic specimens will be specified in the laboratory manual. Any leftover study tissue or blood samples may be stored for future research studies at the behest of the study sponsor. The subjects will consent to the future use of samples in the informed consent form for the study. All future use of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the

Institutional Review Board (IRB) according to its established policies, whether the specimens are stored in a central site or at a local institution or in a virtual repository.

4.2 Study Enrollment

4.2.1 Number of Patients

Approximately 71 patients evaluable for response are anticipated to enroll in this study at medical centers in the United States.

4.2.2 Registration

When the trial site identifies a patient suitable for screening, the site may wish to contact the study chair or designee to ensure a slot is available for inclusion. Screening activities may begin only once written informed consent has been obtained.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after the consent date.

The Vanderbilt-Ingram Cancer Center (VICC) Multi-Institutional Coordinating Center (hereafter referred to the as "the Coordinating Center") will coordinate enrollment onto the study. Once the Coordinating Center confirms eligibility and approves enrollment onto the study, it will provide enrollment confirmation and assigned patient ID numbers.

To enroll a patient onto the study, the enrollment packet should be submitted to the Coordinating Center for eligibility confirmation and enrollment prior to the initiation of protocol therapy.

The enrollment packet includes:

- Enrollment Form
- Eligibility Checklist
- Signed patient consent form
- Eligibility supporting documents such as pathology reports, laboratory tests, etc.

The enrollment packet should be submitted via secure email transfer or fax using the contact information listed on the Enrollment Form.

Issues that would cause treatment delays should be discussed in advance with the study chair. If a participant does not receive protocol therapy following confirmation of eligibility within a reasonable time period in the judgment of the study chair as evaluated on a case-by-case basis, the participant may become ineligible and may be cancelled from the study. Such patient would have to undergo re-screening in order to possibly participate in the study. Any requests for eligibility clarification must be approved in writing by the study chair. Departures from the protocol will not be implemented without agreement from the study chair and prior review and written approval from the Ethics Committee (EC)/IRB, except where necessary to eliminate an immediate hazard to the patient. No protocol waivers will be allowed.

4.2.3 Screen-Failures

A patient found not eligible for the trial after giving informed consent is considered a screening-failure. The enrollment form must be completed and sent to the study chair or designee to confirm the outcome of the screening process.

Re-screening of a patient is allowed.

4.2.4 Replacement of Patients Who Discontinue Early

If a patient discontinues study treatment for reasons clearly not related to study treatment, after completing less than 4 planned azacitidine treatments, or less than 2 planned infusions of pevonedistat over the first 28 days after initiating treatment with azacitidine/pevonedistat on Cycle 1, Day 1, then that patient will be considered not evaluable for response to study treatment and may be replaced with a new patient.

4.3 Duration of Study

It is anticipated that patients will begin protocol-indicated treatment within 28 days after signing consent and will receive study treatment every 28 days until progression of disease, unacceptable toxicity, revocation of consent, or until 12 months of treatment have been received. Treatments may be delayed to allow time for recovery from unanticipated adverse events as described in Section 6.2. Patients achieving complete or partial remission or hematologic improvement (CR,PR, or HI) will be allowed to continue study therapy upon

discussion with the study chair and Takeda. The criteria for patient discontinuation are listed in Section 6.11.

Patients should be assessed when it is decided the patient will no longer receive treatment with azacitidine/pevonedistat; and assessed again 30 days (+14 days) after patient's final treatment with azacitidine/pevonedistat.

Subsequently, each patient will be followed for survival every 3 months (± 14 days) after patient's final treatment with azacitidine/pevonedistat until death, end of the study, until patient withdraws consent, or for a maximum of 1 year after a patient's final treatment with azacitidine/pevonedistat – whichever comes first. Contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

The duration of the study is expected to be 2 years, allowing 12 months for accrual and 12 months for follow up.

5. STUDY POPULATION

Questions regarding patient eligibility must be addressed and resolved by the investigator or designee in consultation with the study chair or designee prior to enrollment.

5.1 Inclusion Criteria

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

1. Signed and dated voluntary written informed consent 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.

2. Male or female ≥ 18 years of age.

3. Morphologically confirmed diagnosis of MDS or MDS/MPN in accordance with WHO diagnostic criteria. (See Section 11.1)

4. ECOG performance status of 0, 1 or 2. (See Section 11.2)

5. Expected survival ≥ 3 months after consenting.

6. Refractory/relapsed disease following DNMTi failure. Refractory disease defined as either 1) failure to achieve an objective response after at least 4 cycles of DNMTi

therapy, or 2) failure to achieve an objective response with clear progressive disease on bone marrow biopsy after at least 2 cycles of DNMTi therapy. Relapsed disease is defined as having progressive disease after achieving an objective response after at least 2 cycles of DNMTi therapy. Progressive disease and response criteria are defined for MDS in Section 11.3 and for MDS/MPN in Section 11.4.

Previous DNMTi therapy may include 5'azacitidine, decitabine, or DNMTi therapy currently in clinical trials (e.g. SGI-110 (guadecitabine), ASTX727 or CC-486).To be considered DNMTi treatment failure, during each prior treatment cycle, patients must have received equivalent to minimum dosing of:

- decitabine 15mg/m^2 daily x 5 days, or
- 5'azacitidine 50mg/m^2 IV/SC daily x 5 days,
- SGI-110 (guadecitabine) 60mg/m^2 SC daily x 5 days, or
- oral DNMTi therapy with ASTX727 20/100mg daily x 5 days, or
- oral DNMTi therapy with CC-486 200mg daily x 14 days.

7. Recovery to ≤ Grade 1 or baseline of any toxicity due to prior systemic treatments, excluding alopecia.

8. Patient consent to collection of fresh bone marrow biopsy and aspirate for exploratory research obtained from a procedure performed no more than 28 days prior to initiating treatment on Cycle 1, Day 1. Requirement for bone marrow biopsy may be waived with approval of the study chair in the event that a bone marrow biopsy cannot be obtained.

9. Clinical laboratory values as specified below:

    - Serum albumin > 2.7 g/dL
    - Total bilirubin ≤ 1.5 x ULN
    - ALT and AST ≤ 2 x ULN
    - WBC ≤ 50,000/μL (use of hyroxyurea is permitted)

- Calculated creatinine clearance ≥ 50 mL/min (per the Cockcroft-Gault formula) (See Section 11.5)

10. Hgb <8g/dL should be transfused to provide adequate tissue perfusion as per the discretion of the investigators and local practice. Rechecking Hgb level prior to start on Cycle 1 Day 1 is not necessary as long as patients do not have inadequate oxygenation, underlying cardiopulmonary compromise, and/or any other reason deemed clinically significant to delay therapy per the investigator.

11. Women of childbearing potential must have a negative serum pregnancy test; and additionally agree to simultaneously use at least 2 methods of effective contraception (see Section 11.6) or abstain from heterosexual intercourse from the time of signing consent, and until 4 months after patient's last dose of protocol-indicated treatment. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.

    WOCBP are defined as those not surgically sterile or not post-menopausal.

    If a female patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for at least 1 year in the absence of an alternative medical cause, then patient will be considered a female of childbearing potential.

    Postmenopausal status in females under 55 years of age should be confirmed with a serum FSH level within laboratory reference range for postmenopausal women.

12. Men, even if surgically sterilized (i.e. status post-vasectomy), who are sexually active with WOCBP must agree to follow instructions for effective barrier contraception (see Section 11.6) from the time of signing consent and until 4 months after last dose of protocol-indicated treatment. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.

5.2 Exclusion Criteria

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

1. Diagnosis of acute myeloid leukemia (i.e. ≥ 20% peripheral or marrow blasts).

2. Any HSCT within 6 months prior to signing informed consent.

3. Any patient who is eligible for HSCT at the time of study screening.

4. Clinically significant graft versus host disease (GVHD) or GVHD requiring initiation of treatment or treatment escalation within 21 days, and/or > Grade 1 persistent or clinically significant non-hematologic toxicity related to HSCT

5. Any previous treatment with pevonedistat or other NEDD8 inhibitor.

6. Treatment with any investigational products within 14 days before the first dose of protocol-indicated treatment.

7. Systemic antineoplastic therapy or radiotherapy within 14 days before the first dose of any study drug.

8. Major surgery requiring general anesthesia within 14 days before the first dose of any study drug or a scheduled surgery during study period. (Placement of a central line or port-a-catheter is acceptable within this time frame and does not exclude the patient.)

9. Treatment with clinically significant metabolic CYP3A inducers within 14 days before the first dose of study drug. Clinically significant CYP3A inducers are not permitted during the study. (See Section **Error! Reference source not found.**)

10. Prolonged QTc interval > 500 msec, calculated according to Fredericia's formula.

11. Known cardiopulmonary disease defined as having one or more of the following:

    - Uncontrolled high blood pressure (i.e. systolic > 180 mmHg or diastolic > 95 mmHg);

    - Symptomatic cardiomyopathy;

    - Ischemic heart disease; Patients with acute coronary syndrome, myocardial infarction, and/or revascularization (e.g. coronary artery bypass graft, stent) within 6 months (24 weeks) of first dose of study drug are excluded; Patients with a history of ischemic heart disease who have had revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll;

- Arrhythmia (e.g. history of polymorphic ventricular fibrillation or torsade de pointes). Patients with symptomatic atrial fibrillation (Afib) incompletely controlled medically, or controlled by device (e.g. pacemaker) or by ablation in the past 6 months are excluded. However, patients with stable AFib for a period of at least 6 months, whose Afib is controlled with medication, or who have a history of paroxysmal AFib are permitted to enroll;

- Implantable cardioverter defibrillator;

- Congestive heart failure (New York Heart Association [NYHA] Class III or IV; or Class II with a recent decompensation requiring hospitalization or referral to a heart failure clinic within 4 weeks before screening),

- Moderate to severe aortic and/or mitral stenosis or other valvulopathy (ongoing). Mild regurgitation is not excluded;

- Pulmonary hypertension.

12. Female patients who are both lactating and breastfeeding, who have a positive serum pregnancy test during screening, or who plan to become pregnant while in the trial or within 90 days after receiving protocol-directed treatment.

13. Active uncontrolled infection. Patients with infection under active treatment and controlled with antibiotics are not excluded.

14. Known Childs class B or C hepatic cirrhosis or severe pre-existing hepatic impairment.

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

16. Known human immunodeficiency virus (HIV) seropositivity.

17. Any serious concurrent condition that could, in the investigator's opinion, significantly interfere with completion of study procedures or protocol compliance.

18. 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).

19. 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).

5.3 Inclusion of Underrepresented Populations

Women and men of all races and ethnic groups are eligible for this trial. There is no bias towards gender or race in the clinical trial outlined.

6. STUDY DRUG

6.1 Study Drug Administration

6.1.1 Azacitidine Subcutaneous Injection or Intravenous Infusion

Each site will obtain azacitidine (VIDAZA) from commercial supply.

On Days 1, 2, 3, 4 and 5 of each 28-day cycle, each patient is scheduled to receive azacitidine at 75 mg/m^2.

On treatment days when patients are scheduled to receive both azacitidine and pevonedistat (i.e. on Days 1, 3 and 5 of each scheduled cycle), administration of azacitidine will be completed BEFORE initiation of pevonedistat treatment.

Azacitidine may be administered either by subcutaneous injection, or a 10-40 minute intravenous infusion, however subcutaneous injection is preferred:

- Before treating a first patient, the local principal investigator at each participating institution will advise the coordinating center as to whether the participating institution will administer azacitidine by subcutaneous injection, or intravenous infusion.

- If an institution elects to be a "subcutaneous" azacitidine site, then each patient at that particular institution must receive azacitidine by subcutaneous injection, until azacitidine is not tolerated by a given patient at the institution – at which time the individual patient may stop receiving subcutaneous azacitidine and start receiving intravenous azacitidine.

For example: A patient receiving SC azacitidine experiences dermatologic/skin intolerance (e.g. Grade 2 injection site reaction is pain or swelling, with inflammation or phlebitis), or any Grade 2 event that is related to intolerance of SC drug administration, may be switched to IV azacitidine.

Please note a switch from intolerable subcutaneous to hopefully tolerated intravenous azacitidine is to occur only on a patient-by-patient basis at the institution. Thus, if one patient at a "subcutaneous" azacitidine institution is switched to intravenous azacitidine, other patients at the "subcutaneous" azacitidine institution should still continue SC azacitidine until they also experience intolerable adverse effects.

- If an institution elects to be an "intravenous" azacitidine institution, then each patient at that particular institution must receive azacitidine by intravenous infusion. (Note that a switch from intravenous to subcutaneous azacitidine administration at a given institution is not intended, and may not occur without discussion and agreement between the local investigator and the study chair.)

Azacitidine will be prepared and administered according to the product label[32].

The amount of azacitidine to be administered will be based on body surface area (BSA).

BSA will be calculated Day 1 of each treatment cycle, and the dose of azacitidine will be modified accordingly if the patient experiences a $> \pm 10\%$ change in body weight relative to the weight used for the most recent BSA calculation.

Azacitidine IV is considered moderately emetogenic therapy. Premedication may include a 5-HT_3 antagonist (i.e. ondansetron, granisetron, etc) and/or dexamethasone or may occur per institutional practice.

According to local institutional guidelines, an infusion (if so administered) may be slowed or stopped and restarted for any suspected or actual infusion-related reaction.

In each 28-day cycle, a maximum of 5 doses of azacitidine should not be exceeded.

Every effort should be made to target infusion timings to be as close to scheduled duration as possible. Interruption and/or prolongation of infusion duration for the purpose of managing a suspected or actual adverse event such as an infusion reaction will not be considered a protocol deviation.

6.1.2 Pevonedistat Infusion

The study will supply pevonedistat to each site.

On Days 1, 3 and 5 of each 28-day cycle, each patient is scheduled to receive pevonedistat at 20 mg/m^2.

On treatment days when patients are scheduled to receive both azacitidine and pevonedistat (i.e. on Days 1, 3 and 5 of each scheduled cycle), pevonedistat will be administered AFTER completion of azacitidine treatment.

Pevonedistat will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

The amount of pevonedistat to be administered will be based on BSA.

BSA will be calculated on Day 1 of each cycle, and the dose of pevonedistat will be modified accordingly if the patient experiences a $> \pm 10\%$ change in body weight relative to the weight used for the most recent BSA calculation.

All patients will receive pevonedistat diluted with 5% dextrose in a 250-mL IV bag via a 60-minute IV infusion.

Pevonedistat should be administered through central or peripheral venous access.

According to local institutional guidelines, the infusion may be slowed or stopped and restarted for any suspected or actual infusion-related reaction.

There are no pre-medications specified by protocol which must be administered prior to a pevonedistat infusion. However, sites may optionally elect a pre-medication regimen if consistent with established local institutional procedures.

All infusion times and details about any optional pre-medications must be recorded. The total time from drug reconstitution to end of infusion must not exceed 6 hours.

Any 2 doses of pevonedistat must be separated by at least 1 calendar day.

In each 28-day cycle, a maximum of 3 doses of pevonedistat should not be exceeded.

Every effort should be made to target infusion timings to be as close to scheduled duration as possible. The infusion may be slowed or stopped and restarted for any actual or suspected associated infusion-related reactions.

6.1.3 Dose Level Summary

In treatment cycles scheduled for 28 days each, all patients will receive azacitidine in combination with pevonedistat. All patients are scheduled to initiate treatment at 75 mg/m^2 azacitidine + 20 mg/m^2 pevonedistat.

If needed for management of potential treatment-related adverse events (see Section 8), a maximum of 2 dose reductions of azacitidine and 2 dose reductions of pevonedistat are allowed. For purposes of this study (and interpretation of the dose reduction summary in Table 6-1 below) dose levels of azacitidine and pevonedistat shall be considered separable and may be individually adjusted as per the dose modification guidelines outlined in the remainder of Section 6.2. Thus, while all patients are scheduled to begin treatment at 75 mg/m^2 azacitidine + 20 mg/m^2 pevonedistat (dose level 0 for both drugs), over time a patient who has experienced treatment-related toxicity requiring dose modifications might be receiving azacitidine at one reduced dose level (e.g. dose level -2), but pevonedistat at another reduced dose level (e.g. dose level -1).

As needed for management of treatment-related toxicity in a given patient, the planned intrapatient dose level reductions are listed below in Table 6-1:

Table 6-1: Summary of Planned Intrapatient Dose Level Reductions for Toxicity Management

Dose Level[a]	Azacitidine S.C. or I.V. Days 1, 2, 3, 4, and 5	Pevonedistat I.V. Days 1, 3 and 5
0	75 mg/m^2	20 mg/m^2
- 1	50 mg/m^2	15 mg/m^2
- 2 (50% reduction)	37.5 mg/m^2 ***	10 mg/m^2 ***
- 3	Discontinue	Discontinue

1 cycle = 28 days

[a] Dose levels of azacitidine and pevonedistat should be considered separable; the dose level of each drug may be independently modified according to the guidelines for management of treatment-related toxicities outlined in Section 6.2.

*** If ongoing treatment-related Grade ≥ 3 adverse event is observed, despite two total permissible dose reductions, the patient should permanently discontinue study treatment. For patients who are deriving clinical benefit after total permissible dose reductions, but who have persistent disease-related Grade ≥ 3 hematologic adverse event requiring dose modification per protocol, further dose modifications may be permitted only upon study chair approval.

Once the dose of either azacitidine or pevonedistat has been reduced, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. A patient will only be allowed to re-escalate after discussion and agreement between the investigator and the study chair (e.g. as part of an appropriate evaluation of a potentially overlapping toxicity between azacitidine and pevonedistat, which after strategic dose reduction is ultimately judged best attributed to one individual drug, but unlikely or not related to the other drug). Further, in the event that the investigator has made appropriate dose reductions, but senses the schedule is too short for a particular patient, schedule may allow for up to 42 days between cycles. Extending the cycle length beyond 42 days will require discussion between the Investigator and the Study Chair and may require additional assessments (e.g. bone marrow biopsy). See section 6.2.1 for more details.

6.2 Dose-Modification Guidelines

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, dated 14 June 2010 and currently locatable via the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

In general, attribution to one or the other individual drug may be difficult due to overlapping toxicities. Thus, it is possible that dose hold/reduction of BOTH azacitidine AND pevonedistat will be necessary. However, if an adverse event can reasonably be attributed (i.e. possibly, probably or definitely related) by the investigator to either azacitidine or to pevonedistat alone, then the dose of the single drug to which an adverse event is attributed may be individually held/reduced at the investigator's discretion (while the other, non-suspected drug is continued without dose hold/reduction).

Unless otherwise addressed within the protocol, events both hematologic and non-hematologic judged by the investigator to be at least possibly related to azacitidine should be managed (e.g. held/reduced/discontinued) according to the azacitidine package insert[32].

At all times, unless otherwise clearly addressed by the protocol, investigator discretion allows the holding, dose reduction or permanent discontinuation of azacitidine and/or pevonedistat, regardless of the severity or duration of an adverse event; the protocol shall

not prevent the medical judgement of the investigator from facilitating appropriate intervention even for an adverse event which may be considered of "low" grade or "brief" in duration. Similarly, in the event that severe disease associated cytopenias are present as demonstrated by a bone marrow biopsy done within 2 cycles (e.g. evidence of a hypercellular marrow in presence of cytopenias), dose modification and treatment interruption instructions with respect to hematologic parameters do not apply, as these hematologic cytopenias are not drug toxicities, but rather, disease-associated features. In this case, the patient may receive treatment if all other parameters required to proceed with therapy are met. Given that relapsed-refractory MDS is a disease with a median OS of 6 months, and is nearly universally associated with damaged bone marrow and pancytopenia, expectations for hematologic toxicity need to be managed appropriately, and relative to expected large burden of disease associated cytopenias. This guidance should be considered in the interpretation of the remainder of Section 6.2.

6.2.1 Treatment Interruption and Delays

Every effort should be made to administer protocol-indicated treatment according to the planned dose and schedule. In the event of significant toxicity, dosing may be interrupted, delayed and/or reduced as outlined below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients must be instructed to notify investigators at the first occurrence of any adverse symptom(s). Dose delays may occur:

Within a cycle:

In general, treatment interruption with either azacitidine or pevonedistat within a cycle should typically occur only if there is an unexpected and/or unacceptable toxicity (e.g. renal or hepatic failure).

A patient experiencing a Grade 3 or 4 non-hematologic adverse event at least possibly related to protocol-indicated treatment (in the opinion of the investigator) should have treatment interrupted. For a Grade 3 or 4 potentially attributable non-hematologic event: HOLD both azacitidine and pevonedistat – REGARDLESS of when the event occurs in the cycle.

Appropriate follow-up assessments should be implemented until adequate recovery occurs. Adequate recovery is defined as improvement to ≤ Grade 1, or to the patient's

baseline value, or to a level considered acceptable after discussion and agreement between the investigator and the study chair.

Upon adequate recovery from a suspected toxicity provoking a dose hold, treatment may be resumed with dose modification (if required) at the discretion of the treating investigator, but only if treatment was delayed by ≤ 2 days. If more than 2 days have elapsed since the dose was scheduled to be given, then that dose should be omitted and should not be made up, but the remainder of the doses in that cycle may be given if ≤ 2 days have elapsed since they were originally scheduled to be administered. If recovery from a non-hematological adverse event, that is at least possibly related to protocol-indicated treatment and that prompts dose interruption within a cycle, does not occur for more than 2 weeks but occurs before the next cycle is scheduled to begin, then DOSE MODIFICATION is required in the subsequent cycle per guidelines outlined below.

If treatment with either or both drug(s) is/are interrupted due to reasons other than toxicity (e.g. scheduling conflict, bad weather), treatment may be resumed in the same cycle if no more than a 3 day gap occurs between interrupted and resumed treatment and the patient is still likely to have clinical benefit as judged by the treating investigator.

For pevonedistat, a minimum of 1 calendar day between any 2 doses should be maintained.

In each cycle, a maximum of 5 doses of azacitidine, and 3 doses of pevonedistat should be administered.

Prior to initiating a new cycle:

Treatment with azacitidine and pevonedistat is scheduled to be repeated every 28 days.

Initiation of a new treatment cycle may be delayed for up to 2 weeks if an adverse event at least possibly related to treatment in the preceding cycle persists. As commonly the case with treatment of MDS with DNMTi, some patients require flexibility with the dosing schedule to allow time for adequate marrow recovery. In the event that (at least) possibly related hematologic toxicity persists as a result of PevAz treatment, then delaying as above is acceptable.

In the event that treatment is delayed due to non-hematologic adverse event, the patient should be evaluated at least once weekly to determine if criteria for retreatment are met: For held therapy to resume, a treatment-related adverse event provoking a dose delay

must have resolved to ≤ Grade 1, to the patient's baseline values, or to a level considered acceptable by the investigator after discussion and agreement with the study chair or their designee.

If the patient fails to meet such criteria for retreatment and/or if treatment is delayed for any reason by more than 2 weeks, initiation of a new cycle of therapy should only occur after written approval is obtained from the study chair.

If treatment is delayed by more than 2 weeks between cycles (i.e. cycle longer than 42 days) due to incomplete recovery from an adverse event that is possibly, probably or definitely related to protocol-indicated treatment (per judgement of the treating investigator), then DOSE MODIFICATION is required per guidelines outlined below. (Incomplete recovery is defined as failure to improve to ≤ Grade 1, or to the patient's baseline values, or to a level considered acceptable after discussion and agreement between the investigator and the study chair.)

6.2.2 Dose Modification General Considerations

Prior to each treatment cycle, patients should be clinically assessed for adverse events (as per Section 8, using the NCI CTCAE v4.03 grading scale dated June 14, 2010).

Protocol-indicated treatment will occur only if a patient's clinical assessment and laboratory test values are acceptable:

- ECOG performance status 0, 1 or 2
- Adequate recovery from any adverse events at least possibly related to azacitidine/pevonedistat treatment during preceding cycles. Unless otherwise defined by the protocol, adequate recovery is defined as improvement to Grade ≤ 1, to the patient's baseline values, or to a level considered acceptable after discussion and agreement between the investigator and the study chair.

If an adverse event is judged by the treating investigator to be probably or definitely attributed to either azacitidine alone, or to pevonedistat alone (but is not attributed to the combination of azacitidine + pevonedistat), then the single drug – either azacitidine OR pevonedistat – to which the adverse event is attributed may be held/reduced individually.

If an adverse event is not reasonably attributable to an individual drug, then BOTH drugs (i.e. azacitidine AND pevonedistat) should be held/reduced.

In order to maintain a consistent inventory of scheduled study procedures across patients, the study calendar for an individual patient will not be paused within a given treatment cycle, but rather may be paused between different treatment cycles for dose delays as necessary (i.e. within a given treatment cycle, the study calendar "clock" will keep running; and any days within a cycle that a patient does not receive protocol-indicated are still to be considered part of the 28-day treatment cycle, during which time any other protocol-indicated assessments should be completed as scheduled and as would otherwise occur in the absence of a treatment delay).

6.2.3 Dosing Guidelines for Hematologic Toxicity

Disease-related cytopenias are expected in this population of patients with MDS who have failed prior therapy with hypomethylating agents. Nearly all patients will enter study with non-functional bone marrow and depressed peripheral blood counts. However, counts may also fall with protocol-indicated treatment. Thus, with respect to hematologic toxicities, drug dose reductions should be limited to cases of persistent cytopenias PERCEIVED or PROVEN to result from reduced bone marrow cellularity (i.e. treatment-related as opposed to disease-related). Doses of azacitidine or pevonedistat do NOT require withholding within a cycle unless the cytopenias are PERCEIVED or PROVEN by the investigator to be secondary to azacitidine or pevonedistat.

Initiation of new cycles may be delayed if count recovery (see Table 6-2) has not occurred and/or may be dose-adjusted based on the degree of count recovery, if persistent cytopenias are PERCEIVED or PROVEN to result from reduced bone marrow cellularity (i.e. treatment-related as opposed to disease-related). In the event that a bone marrow biopsy is conducted and reveals decrease in cellularity consistent with PevAz induced marrow insult, PevAz should be held until this insult has recovered or the dose adjusted based on the degree of count recovery as outlined in Table 6-4 andTable 6-4. If, however, failure to recover counts completely is PERCEIVED or PROVEN to be due to the primary disease without decreases in marrow cellularity, therapy may continue.

Delayed initiation of a new cycle by ≥ 2 weeks due to lack of recovery from a treatment-related hematologic toxicity will require dose reduction (if treatment resumes). Recovery from hematologic adverse events of neutropenia and thrombocytopenia, based on peripheral blood counts, is defined below in Table 6-2:

Table 6-2: Definition of Recovery from Hematologic Toxicity

"RECOVERY" from respective hematologic toxicity is defined as:	For patients with "RESERVE" baseline counts before Cycle 1 defined as: *ANC ≥ 1500 /mm³ - and - Platelets ≥ 100,000 /mm³*	For patients with "SUPPRESSED" baseline counts before Cycle 1 defined as: *ANC < 1500 /mm³ - or - Platelets < 100,000 /mm³*
Neutrophil count	ANC > 500 /mm³ *and* ≥ 50% of baseline ANC	ANC > 100 /mm³ *or* ≥ 50% of baseline ANC
Platelet count	Platelets > 50,000 /mm³ *and* ≥ 50% of baseline platelet count	Platelets > 25,000 /mm³ *or* ≥ 50% of baseline platelet count

Abbreviations: ANC absolute neutrophil count

For patients with "suppressed" baseline counts (as per Table 6-2) there will be no mandated dose reduction of azacitidine or pevonedistat, unless further reduction in ANC and/or platelets from baseline are PERCEIVED or PROVEN to result from reduced bone marrow cellularity (i.e. treatment-related as opposed to disease-related). If full recovery from perceived or proven treatment-related hematologic toxicity has not occurred by Day 42, treatment may continue (at the discretion of the treating physician) with dose reductions of azacitidine and/or pevonedistat as outlined in 3.

Table 6-3: Guide for Dose Modifications for Treatment-Related Hematologic Toxicity in Patients with *Suppressed Baseline Blood Counts*[a]

DEGREE OF COUNT RECOVERY Current ANC and/or platelet count:	DOSE LEVEL REDUCTION[b]	
	AZACITIDINE	PEVONEDISTAT
<50% decreased from baseline counts	Dose Level 0	Dose Level 0
50-75% decreased from baseline counts	Dose Level -1	Dose Level 0
>75% decreased from baseline counts	Dose Level -2	Dose Level -1

Abbreviations: ANC absolute neutrophil count

[a] As defined in Table 6-2, patients with suppressed baseline counts have an ANC < 1500 /mm³ or Platelets < 100,000 /mm³ prior to initiation of protocol-indicated treatment.

[b] Dose Levels of azacitidine and pevonedistat are considered separable and may be modified independently. Doses of each drug are listed with corresponding dose level in Table 6-1.

Patients with "reserve" baseline counts (as per Table 6-2) who have significant reductions in ANC and/or platelets (>50% reduced as compared to baseline counts) that are AT LEAST PROBABLY related to protocol-indicated treatment and that persist at the start of the next cycle, may require dose delay or modification of azacitidine and/or pevonedistat, based on degree of count recovery (see Table 6-4).

Table 6-4: Guide for Dose Modifications for Hematologic Toxicity in Patients with *Reserve Baseline Blood Counts*[a]

<table>
<tr><th colspan="3">Blood Counts at Next Cycle Day 1 Assessment</th><th colspan="4">DOSE LEVEL REDUCTION[b] to be taken upon peripheral count "RECOVERY" (as defined above in Table 6-2) and with respect to:</th></tr>
<tr><th>ANC (/mm^3)</th><th>Platelet (/mm^3)</th><th>Relative to Baseline Counts</th><th colspan="2">AZACITIDINE</th><th>PEVONEDISTAT</th></tr>
<tr><td colspan="3">> 1500 and > 50,000</td><td colspan="2">Dose Level 0</td><td>Dose Level 0</td></tr>
<tr><td colspan="3">≤ 1500 or ≤ 50,000 and <50% reduced</td><td colspan="2">Dose Level 0</td><td>Dose Level 0</td></tr>
<tr><td colspan="3" rowspan="5">≤ 1500 or ≤ 50,000 and ≥ 50% reduced</td><td colspan="4">Delay treatment up to 2 weeks for recovery. Then,</td></tr>
<tr><td colspan="2">If counts are:</td><td colspan="2">Treat with:</td></tr>
<tr><td>ANC</td><td>Platelet</td><td>AZA</td><td>PEV</td></tr>
<tr><td>>1500 and >50,000</td><td>Dose Level 0</td><td>Dose Level 0</td></tr>
<tr><td>500 - 1500 or 25 - 50,000</td><td>Dose Level -1</td><td>Dose Level 0</td></tr>
<tr><td><500 or <25,000</td><td colspan="2">Reassess disease; Discuss with Study Chair[c]</td></tr>
</table>

Abbreviations: ANC absolute neutrophil count

[a] As defined in Table 6-2, patients with reserve baseline counts have an ANC ≥ 1500 /mm^3 or Platelets ≥ 100,000 /mm^3 prior to initiation of protocol-indicated treatment.

[b] Dose Levels of azacitidine and pevonedistat are considered separable and may be modified independently. Doses of each drug are listed with corresponding dose level in Table 6-1.

c If a patient with reserve baseline counts, continues to have significant cytopenias (ANC < 500 /mm^3 or Platelets < 25,000 /mm^3 at day 42 of any cycle, the Investigator should reassess the disease status with a bone marrow biopsy. Consideration for continuation of protocol-indicated treatment with dose adjustment or discontinuation of treatment should be discussed with the Study Chair.

NOTE: The azacitidine dose modifications outlined above based on peripheral blood counts reflect current clinical practice and are appropriate guidelines for the study. Note that the dose modifications of azacitidine proposed in this protocol differ from the package insert[32], which requires assessment of bone marrow cellularity for dose modification of patients whose baseline counts are white blood cells (WBC) < 3.0 x 10^9/L, ANC < 1.5 x 10^9/L, or platelets < 75.0 x 10^9/L. However, it is not standard clinical practice to perform bone

marrow biopsy in MDS patients exclusively for dose modification (unless severe persistent cytopenias occur, as noted above). If clinically indicated any time in the study (e.g. if counts do not recover in the expected time frame or if leukemic progression is suspected), bone marrow evaluation during this study may be performed to establish whether continued myelosuppression is related to progressing leukemic infiltration or treatment-related bone marrow aplasia.

Patients with worsening treatment-related cytopenias despite 2 dose level reductions of either azacitidine or pevonedistat should permanently DISCONTINUE protocol-indicated treatment. If a patient with disease-related hematologic adverse event(s) is receiving clinical benefit but experiences ongoing neutropenia and/or thrombocytopenia despite 2 dose level modifications, further dose modifications may be considered but must be approved by the study chair.

Patients who require dose modifications due to hematologic adverse events but who then have improvement in blood counts in subsequent cycles may re-escalate treatment at the discretion of the treating physician. If doses of azacitidine and/or pevonedistat are re-escalated and the patient has a subsequent treatment-related hematologic adverse event, treatment should continue at the modified dose level(s) and should not be re-escalated again.

For ANC < 100 /mm^3 with or without neutropenic fever, granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) may be administered between cycles at the discretion of the investigator only if BM blasts are ≤5% and must be clearly documented in the clinical notes and case report form (CRF).

All dose modifications/adjustments must be clearly documented.

Dose modifications and/or holding are not required for other hematologic adverse events (i.e. other than neutropenia and thrombocytopenia). Note: for Grade >2 anemia, supportive measures with red blood cell transfusion should be considered.

6.2.4 Dosing Guidelines for Impaired Renal Function/Electrolyte Abnormalities

If serum creatinine or BUN rises ≥ 1.5 ULN or serum bicarbonate level is < 20 mmol/L, the next cycle should be delayed until values return to normal or baseline.

If the increase in serum creatinine, BUN or bicarbonate is at least probably related to protocol-indicated treatment, then:

- For first occurrence of elevated creatinine, then the dose of azacitidine should be reduced at least 1dose level (i.e. 25% reduction) on the next treatment cycle and pevonedistat should also be reduced by 1 dose level.

- For second occurrence of renal toxicity at least probably related to PevAz treatment, azacitidine dose will be reduced to dose level -2 (i.e. 50% reduced), and pevonedistat will also be further reduced by 1 dose level.

- Treatment should be discontinued with a third occurrence despite maximum support and allowable dose reductions.

In the event that there are renal toxicities as noted above that cannot be attributed to study drug (e.g. viral gastroenteritis and dehydration leading to acute kidney injury after completion of drug administration) these dose modifications need not be applied, and patient may continue at the same dose level when recovered from the unrelated insult.

6.2.5 Dosing Guidelines for Abnormalities in 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 elevations of transaminases and bilirubin Grade ≥ 2 that occur on or after Cycle 1 Day 3, further pevonedistat treatment should be withheld until elevations in the AST/ALT return to Grade ≤ 1 and bilirubin ≤ 1.5 x ULN or to the patient's baseline values.

For elevated LFTs of Grade 2 or 3 that occur on or after Cycle 1 Day 3, pevonedistat dose may be resumed without dose reduction once LFTs have recovered as defined above. 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. If recovery takes more than 2 days, subsequent doses of pevonedistat in that cycle should only be given if the patient is still likely to have clinical benefit as judged by the treating investigator. If Grade 2 or 3 elevations in LFTs persist, requiring either significant treatment delays (i.e. >2 days) or missed doses, or recur within the same cycle, no further pevonedistat doses should be administered in that cycle and dose modification of pevonedistat should be considered in subsequent cycles.

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 $\leq$

1, and/or elevated bilirubin returns to ≤1.5×ULN or to the patient's baseline level, then pevonedistat may be restarted at the next cycle at a reduced dose. If no other cause for the Grade 4 elevation in LFTs was identified other than pevonedistat, then the dose of pevonedistat should not be re-escalated. If, however, an alternative cause for the LFT abnormality was suspected and can be removed with no LFT changes observed at the reduced pevonedistat dose, pevonedistat may be re-escalated in a subsequent cycle. If a patient is re-challenged with a higher dose of pevonedistat and again experiences LFT abnormalities that require dose modification, then the patient should not be re-challenged at the higher dose again.

If a patient experiences both Grade ≥ 3 elevations in serum transaminases and Grade ≥ 2 elevation in bilirubin with no evidence of cholestasis (i.e. serum alkaline phosphatase ≤2xULN) with no other cause of hepatotoxicity identified, then the patient should permanently discontinue study treatment. If alternative causes are suspected, these should be investigated and potentially confounding factors should be removed prior to subsequent treatment on study. If potentially confounding factors are removed and subsequent treatment is given with dose reduction, the patient should be removed from the study if a second occurrence of Grade ≥ 3 elevations in serum transaminases with Grade ≥ 2 elevation in bilirubin and no evidence of cholestasis is noted.

If the Grade ≥ 3 elevation in serum transaminases or bilirubin was at least probably related to PevAz treatment and treatment will be resumed after adequate recovery as defined above, dose modifications should occur according to the following guidelines:

Table 6-5: Guide for Dose Level Modifications for Hepatotoxicity

Occurrence	**Grade 2 or 3 elevations in LFTs** (requiring significant treatment delay or missed doses; treatment may resume within a cycle if adequate recovery is achieved)		**Grade ≥ 4 elevations in LFTs** (pevonedistat held for remainder of the cycle; treatment may resume with dose reduction in subsequent cycle if adequate recovery is achieved)	
	AZACITIDINE	**PEVONEDISTAT**	**AZACITIDINE**	**PEVONEDISTAT**
First occurrence:	Dose level 0	Dose level 0	Dose level 0	Dose level -2
Second occurrence:	Dose level 0	Dose level -1	Dose level -2	Dose level -2
Third occurrence:	Dose level -1	Dose level -1	Discontinue	Discontinue

In the event that there are liver enzyme elevations or bilirubin elevations as noted above that cannot be attributed to study drug (eg Hepatitis A infection at D24 in cycle) these dose modifications need not be applied, and patient may continue at the same dose levels of pevonedistat and azacitidine when they have recovered from the unrelated insult.

6.2.6 Dosing Guidelines for Hypophosphatemia

If hypophosphatemia is Grade ≥ 3, pevonedistat 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.

6.2.7 Guidance for Management of Patients with WBC Counts > 50,000/µL

One patient died of AML complicated by leukostasis within hours after receiving the first dose of pevonedistat. This patient experienced rapidly increasing blast counts (to levels greater than 100,000/µL) before receiving the first dose of pevonedistat on C1D1. This patient was not treated with hydroxyurea before receiving treatment with pevonedistat. Patients with AML who experience extremely high leukemic blast cell count are at high risk of leukostasis, an AML complication characterized by an extremely elevated blast cell count causing symptoms of decreased tissue perfusion. To mitigate the risk of leukostasis, Study C15003 was amended to require that patients have a WBC count ≤ 50,000/µL at screening and before pevonedistat dosing during the first cycle of treatment.

In response to this event, AML clinical study protocols were updated to include a monitoring and treatment plan for leukocytosis and an exclusion criterion requiring a WBC count below 50,000/µL at screening and on pevonedistat dosing days in Cycle 1. For patients who develop symptoms of leukostasis while on the study, pevonedistat treatment should be withheld until the leukostasis symptoms are controlled. Treatment of leukostasis symptoms may include leukapheresis and hydroxyurea administration per study site institutional guidelines. When the WBC count of the patient is < 50,000/µL and symptoms are improved, pevonedistat treatment may be restarted after consulting with the project clinician.

6.2.8 Dosing Guideline for Other Non-Hematologic Toxicities

If an adverse event can be reasonably attributed (i.e. probably or definitely attributable) to either azacitidine or pevonedistat alone, the dose of the single drug to which the adverse event is attributed may be reduced individually at the investigator's discretion. If the

adverse event cannot be reasonably attributed to a single drug, then the doses of both azacitidine and pevonedistat should be reduced with each event.

In general, Grade ≥ 3 non-hematologic adverse events other than previously described in Sections 6.2.4 through 6.2.7 and at least possibly attributed to protocol-indicated treatment will require modification of azacitidine and/or pevonedistat. However, for nausea, vomiting, and diarrhea, Grade ≥ 3 symptoms must persist ≥ 3 days despite maximal supportive medical therapy (e.g. intravenous fluids, anti-emetics, anti-diarrheals) per institutional guidelines to require dose modification.

Guidelines for dose modifications for Grade ≥ 3 non-hematologic toxicities other than previously described in Sections 6.2.4 through 6.2.7 include:

- Treatment will be withheld until the toxicity provoking the dose hold has resolved/reduced to Grade ≤ 1, returned to the patient's baseline value, or returned to a level that is acceptable to the patient and treating investigator with the potential for clinical benefit (the last scenario requiring discussion and agreement between the treating investigator and study chair).

- For a first episode, azacitidine and/or pevonedistat should be decreased by 1 dose level.

- For a second episode, azacitidine and/or pevonedistat should be further decreased by 1 dose level.

- For a third episode, azacitidine and/or pevonedistat should be permanently discontinued.

A maximum of two dose reductions are allowed. In the event of a third occurrence of non-hematologic adverse event despite maximum supportive measures and despite 2 dose reductions, patients must permanently discontinue study treatment.

6.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Acetaminophen may be used judiciously and should not exceed a dose of 2 grams in 24 hours.

- Clinically significant CYP3A4 inducers are excluded within 14 days before first dose of pevonedistat and during the study (see Section **Error! Reference source not found.**).

- Chronic continuous corticosteroids (e.g. dexamethasone) should not be used because of their CYP3A-inducing effects; however, acute administration, for example as an anti-emetic or to control other side effects, is permissible. Topical/nasal formulations (such as Nasonex) may be used due to minimal systemic absorption.

- Patients must have no known prior history of amiodarone in the 6 months prior to the first dose of pevonedistat.

- Anticoagulants are excluded if they prevent obtaining of bone marrow samples, or if they could not be temporarily held if the platelets fall below 50,000 /mm^3 or if there is clinically significant bleeding.

- Systemic antineoplastic therapy (other than protocol-indicated treatment) is excluded within 14 days before the first dose of azacitidine/pevonedistat and during the study.

- Any definitive anticancer treatment with activity against MDS or MDS/MPN is excluded within 14 days before the first dose of azacitidine/pevonedistat and during the study.

- Any investigational agent (other than azacitidine/pevonedistat) for the treatment of MDS or MDS/MPN is excluded during the study.

- Known BCRP inhibitors (i.e. cyclosporine and eltrombopag [Promacta]) are generally excluded during the study but may be used as specified in Section 6.4.

- Myeloid growth factors (e.g. G-CSF, GM-CSF) should not be routinely used, but may be administered in the event of severe neutropenia with or without fever at the discretion of the treating physician. In this circumstance, use of myeloid growth factors must be clearly documented in the clinical notes and CRF.

- Radiation therapy excluded within 14 days before the first dose of any study drug and during the study.

6.4 Permitted Concomitant Medications and Procedures

The following medications and procedures are allowed during the study:

- Antiemetics may be administered according to institutional guidelines.
- Anticoagulants are permitted as long as they do not interfere with obtaining a bone marrow specimen but should be discontinued at least temporarily if platelets fall below 50,000 /mm^3 or if there is clinically significant bleeding. In the event of bleeding, anticoagulant reversal agents may be used per standard practice.
- Antiplatelet therapy is permitted, unless its use prevents the obtaining of bone marrow samples.
- Known BCRP inhibitors (i.e. cyclosporine and eltrombopag [Promacta]) permitted only if the patient's clinical condition requires the use of a known BCRP inhibitor. Ophthalmic formulations may be used due to minimal systemic absorption. The patient may receive it 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 the BCRP inhibitor 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.
- Nephrotoxic medications, including nonsteroidal anti-inflammatory drugs, should be used with caution. Alternative concomitant non-nephrotoxic medications should be used whenever possible.
- Platelet transfusion: Platelet transfusion(s) may be administered per institutional practice if deemed clinically necessary by the patient's study physician. The transfusion(s) may be administered irrespective of the timing of protocol-indicated treatment. Each transfusion episode, including the type of transfusion (platelet), should be recorded.
- Red blood cell transfusion: For all patients with anemia, and especially for patients with hemoglobin values < 8 g/dL during the conduct of the study, consideration should be given for red blood cell transfusions based on the patient's risk of

inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guideline.

RBC transfusions (if deemed clinically necessary by the patient's study physician) may be administered irrespective of the timing of protocol-indicated treatment per institutional practice. Each transfusion episode, including the type of transfusion (red blood cell), should be recorded.

- Hydroxyurea is permitted to lower white blood cell counts for patients with rapidly proliferating disease

- Any other supportive care medications are also permitted, unless specifically excluded.

6.5 Precautions and Restrictions

Pregnancy

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 potential and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or

- Surgically sterile, or

- If they are of childbearing potential, agree to practice 2 effective methods of contraception (see Section 11.6), at the same time, from the time of signing the informed consent through 4 months after the last dose of protocol-indicated treatment, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

Male patients, even if surgically sterilized (i.e. status post vasectomy) must agree to 1 of the following:

- Practice effective barrier contraception (see Section 11.6) during the entire study treatment period through 4 months after the last dose of protocol-indicated treatment, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.

6.6 Management of Clinical Events

6.6.1 Management of Hemodynamic Compromise

It is essential that patients receiving azacitidine and pevonedistat are carefully evaluated at screening and before each treatment dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration.

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

For all patients with anemia, and especially for those with hemoglobin values < 8 g/dL at screening or during the conduct of the study, RBC transfusions should be considered before azacitidine/pevonedistat dosing based on the risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines; each RBC transfusion should be recorded in the eCRFs.

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

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

6.6.2 Management of Extravasation

Based on nonclinical findings as detailed in the IB[22], 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.

6.7 Description of Investigational Agents

6.7.1 Description of Azacitidine

Azacitidine (VIDAZA) is a nucleoside metabolic inhibitor that is FDA approved for MDS and CMML.

A pyrimidine nucleoside analog of cytidine, azacitidine is believed to exert antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow.

6.7.2 Description of Pevonedistat

Pevonedistat (also known as MLN4924) is a first-in-class small molecule inhibitor of NAE under development for the treatment of malignancies, including solid tumors and hematologic malignancies. The NEDD8 conjugation pathway is involved in the UPS responsible for much of the regulated protein turnover in the cell[18,19].

6.8 Preparation, Reconstitution, and Dispensing

Azacitidine and pevonedistat should be stored, prepared for use and administered according to procedures consistent with the azacitidine product label[32] and pevonedistat IB[22]; a brief overview of these currently available details is presented below in this section. On treatment days when patients are scheduled to receive both azacitidine and pevonedistat (i.e. on Days 1, 3 and 5 of each scheduled cycle), administration of azacitidine will be completed BEFORE initiation of pevonedistat treatment.

6.8.1 Azacitidine Preparation, Reconstitution and Dispensing

For detailed preparation instructions, please see the product label[32].

6.8.1.1 Reconstitution for Subcutaneous Administration

Azacitidine should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/mL. Do not filter the suspension after reconstitution. Doing so could remove the active substance.

6.8.1.2 Preparation for Immediate Subcutaneous Administration

Doses greater than 4 mL should be divided equally into 2 syringes.

The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

6.8.1.3 Preparation for Delayed Subcutaneous Administration

The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately.

When azacitidine is reconstituted using water for injection that has not been refrigerated, the reconstituted product may be held under refrigerated conditions (2-8°C, 36-46°F) for up to 8 hours.

When azacitidine is reconstituted using refrigerated (2-8°C, 36-46°F) water for injection, the reconstituted product may be stored under refrigerated conditions (2-8°C, 36-46°F) for up to 22 hours.

After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

6.8.1.4 Subcutaneous Administration

To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved.

Azacitidine suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each

injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

6.8.1.5 Reconstitution for Intravenous Administration

Reconstitute the appropriate number of azacitidine vials to achieve the desired dose.

Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw the required amount of azacitidine solution to deliver the desired dose and inject into a 50 -100 mL infusion bag of either 0.9% sodium chloride solution or Lactated Ringer's solution.

6.8.1.6 Intravenous Solution Incompatibility

Azacitidine is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of azacitidine and should therefore be avoided.

6.8.1.7 Intravenous Administration

Azacitidine solution is administered intravenously. Azacitidine reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution. Administer the total dose over a period of 10 - 40 minutes.

6.8.2 Pevonedistat Preparation, Reconstitution and Dispensing

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

The specified number of pevonedistat injection drug product vials should be removed and allowed to equilibrate to room temperature prior to dilution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The vial must not be shaken at any time during dose preparation.

Using aseptic technique, the appropriate volume of drug should be withdrawn from vial(s), then injected into a 250-mL IV bag containing 5% dextrose solution, and then gently inverted repeatedly to mix. All patients are scheduled to receive pevonedistat diluted with 5% dextrose in a 250-mL IV bag via a 60-minute IV infusion.

The pevonedistat (pevonedistat-003 Injection) prepared IV bag must be used within 6 hours (time to the end of an injection) if stored at ambient temperature. Alternatively, the prepared IV bag is chemically stable and may be stored for up to 24 hours at 2°C to 8°C. After 24 hours of storage at 2°C to 8°C, the prepared IV bag must be used within 6 hours (time to the end of an injection) upon coming to ambient temperature.

The bag, needle, and syringe must be disposed of in a proper biohazard container.

6.9 Packaging and Labeling

6.9.1 Packaging of Azacitidine

Each site will obtain azacitidine from commercial supply. Azacitidine for injection is typically available as a lyophilized powder in 100 mg single-use vials.

6.9.2 Packaging of Pevonedistat

The study will supply pevonedistat to each site.

Pevonedistat is typically provided in 10 mL glass vials at a concentration of 10 mg/mL.

The drug product is labeled pevonedistat (pevonedistat-003 Injection). Pevonedistat injection drug product formulation consists of 10 mg/mL (as free base) of pevonedistat HCl in an aqueous solution of 7.45 mg/mL citric acid (anhydrous), 3.29 mg/mL trisodium citrate dihydrate, and 100 mg/mL ß-Cyclodextrin sulfobutyl ether (Captisol®) at pH 3.3. Each USP Type I glass vial normally 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.

Full details are available in the IB[22]

6.10 Storage, Handling, and Accountability

6.10.1 Handling and Storage of Azacitidine

Store unreconstituted vials at 25° C (77° F); excursions permitted to 15-30° C (59-86° F).

6.10.2 **Handling and Storage of Pevonedistat**

Vials of pevonedistat (pevonedistat-003 Injection) are to be stored at 2°C to 8°C. Pevonedistat injection is stable at ambient temperature for 8 hours before dilution. All investigational supplies are to be kept in a secure area with controlled access.

6.10.3 **Drug Accountability and Compliance Check**

The investigator is responsible for ensuring accountability for azacitidine and pevonedistat, including maintenance of appropriate drug accountability records.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The amount of drug to be administered will be based on BSA, as described in Section 6.1.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be maintained by the study site.

A pharmacist or designee will maintain applicable records of drug receipt, drug preparation, and dispensing, including the applicable lot numbers, and total drug administered in milliliters and milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

Drug accountability records should include a full inventory of azacitidine and pevonedistat including:

- Confirmation of azacitidine and pevonedistat delivery to the trial site
- Record of each dose azacitidine and pevonedistat dispensed
- Return of unused pevonedistat to the study chair or designee, or documentation of destruction at site (if drug destruction by the site is authorized by the study chair or designee).

Records should specify dates, quantities, batch numbers, use-by dates and patient numbers, as applicable.

The Investigator, or designee, should maintain records that adequately document:

- That the patients were provided the doses specified by the clinical trial protocol, and

- That all pevonedistat provided by the study was fully reconciled.

6.11 Termination of Treatment and/or Study Participation

6.11.1 Discontinuation of Study Treatment

Azacitidine and pevonedistat will be discontinued simultaneously (e.g. if there is an adverse event prohibiting further treatment with either individual drug, or if there is disease progression).

The visit schedule for the treatment period will apply until azacitidine and pevonedistat have both been permanently discontinued. Once this has occurred, an EOT visit is intended within 14 days after the decision to permanently discontinue protocol-indicated treatments and before any subsequent anti-cancer therapy.

After EOT, the patient will continue to be followed until 30 days (+14 days) after the last dose of azacitidine/pevonedistat, at which time Follow-Up must be completed.

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.

The patient must discontinue treatment with pevonedistat and azacitidine in the event of any of the following:

- The maximum duration of treatment in the study will be 12 months, unless it is determined, after discussion and agreement between the investigator and the study chair, that a patient would derive benefit from continued therapy beyond 12 months.
- Patient withdraws consent to participate.
- Occurrence of an AE considered by the investigator to require treatment discontinuation.
- Adverse event requiring discontinuation as outlined in Section 6.2.
- Initiation of subsequent anti-cancer therapy or hematopoietic stem cell transplant.
- Progressive Disease (PD). [Note: patients with PD based on an increase in peripheral or bone marrow blast counts may remain on the study, following discussion and agreement between the investigator and the study chair, if it is judged

that the patient is deriving clinical benefit and has not progressed to acute leukemia (i.e. blast count > 20%).]

- Treatment failure or clinical deterioration not meeting the criteria for PD, but considered by the investigator to require treatment discontinuation.

- Requirement for a significant surgical procedure.

  Note: Patients requiring a minor surgical procedure (e.g. port placement, skin abscess drainage) may continue at the investigator's discretion following discussion with the study chair or designee. A brief interruption in therapy may be considered.

- An intercurrent illness which, in the opinion of the investigator, would prevent completion of trial-related evaluations.

- The investigator judges it necessary due to medical reasons.

- Necessary use of prohibited concomitant medication, as defined in Section 6.3.

- The patient becomes pregnant during treatment. (Cases of pregnancy that occur during maternal or paternal exposures to study treatment should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.)

- Significant deviation from the protocol or eligibility criteria. Such patients will be considered protocol violations and may be discontinued from treatment after discussion with the study chair.

- Noncompliance with trial procedures may require discontinuation after discussion with the study chair.

- Patient withdrawal of consent and election to discontinue treatment. (Patients may leave the trial at any time for any reason if they wish to do so, without any consequences.)

- Decision by suppliers to modify or discontinue the availability, development or manufacture of azacitidine and/or pevonedistat.

- Termination of the trial by the study chair or others.

At the time of treatment discontinuation, all study procedures outlined for the End-of-Treatment visit should be completed. The primary reason for treatment discontinuation should be recorded in the source documents and CRF. At the time of withdrawal, all study procedures outlined for the End of Treatment visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

6.11.2 **Withdrawal from Study**

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or study chair for safety, or behavioral reasons; or the inability of the subject to comply with the protocol-required schedule of study visits or procedures, or an inability to maintain voluntary informed consent. The EOT and the Follow-Up visits should be performed to the extent possible and the investigator should ensure any SAE is followed as described in Section 8.

Reasons for withdrawal from the study might include but are not limited to any of the following:

- The patient withdraws consent to participate in treatment, follow-up, or survival monitoring.
- The Investigator judges it necessary due to medical reasons.
- Subject is lost to follow-up.
- A maximum of 1 year of survival monitoring elapses after patient's last dose of azacitidine/pevonedistat.
- Study is terminated for any reason.

7. STATISTICAL AND QUANTITATIVE ANALYSES

The primary objective of this single-arm, phase II clinical trial is to determine if the combination of pevonedistat and 5'azacitidine can significantly improve the median survival for patients who fail previous therapy with typical DNMTi therapy.

7.1 Statistical Methods

7.1.1 Determination of Sample Size

Median survival in this patient population was 5.6 months[27]. We assume a one-side type I error rate, 12 month accrual and at least 12 months of follow-up for each patient. Assuming exponential survival, 71 patients provide 81% power to detect ($p<0.05$) a hazard ratio of 0.72 or smaller. This represents a 2.2 month improvement in median survival to 7.8 months. Power calculations were conducted using the one-arm survival power estimation tool provided by Cancer Research and Statistics (http://www.crab.org).

7.1.2 Populations for Analysis

Our primary analysis will be based on a modified intent-to-treat (mITT) population defined as any eligible patient who receives at least one dose of treatment. Primary safety, PG and PhD analyses will also be based on this mITT population.

7.1.3 Procedures for Handling Missing, Unused, and Spurious Data

Missing data will be imputed using multiple imputation with predictive mean matching.

7.1.4 Demographic and Baseline Characteristics

Continuous variables (e.g. age) will be summarized using the minimum, 25th, 50th, 75th percentiles and the maximum value. Means and standard deviations will be provided for appropriately distributed (i.e. Gaussian) data. Ninety-five percent confidence intervals will be provided for all point estimates. Distributions of continuous variables will be compared using appropriate parametric group tests (e.g. two-sample t-test, ANOVA, simple linear regression, or linear mixed models) or their nonparametric analogues (e.g. Wilcoxon rank sum test, Kruskal Wallis test, complete information proportional odds model). Categorical variables will be summarized in frequency tables. The chi-square test will be used to compare the distribution of these variables between (among) treatment groups or other important subgroups using the chi-square test. Multi-variable and longitudinal analysis will be conducted using standard logistic and proportional odds regression or with generalized linear and non-linear mixed models as appropriate

7.1.5 Efficacy Analysis

Our primary endpoint is overall survival, defined at the time from date of enrollment to death for any reason. Patients alive at last follow-up will be censored at the date of last follow-up. Secondary efficacy endpoints include time-to-progression and best objective

response. Time to progression is defined as the time from enrollment to progression or death for any reason. Patients alive and progression-free on the date of their last follow-up will be censored. Best objective response is defined as a classification of CR, PR, or HI (as defined in Sections 11.3 and 11.4) prior to progression of disease.

Assuming exponential survival, Lawless (1982) provided tests and confidence intervals for the mean ($\theta = T/r$) of the exponential survival distribution where T is the total of all observed and censored lifetimes and r is the number of patients who expire during followup. The distribution of $\phi = \theta^{-1/3}$ in small samples is more closely normally distributed. We will reject the null hypotheses that overall survival is equal to our historical estimate (median OS=5.6 months) if $Z = (\varphi\hat{} - \varphi)/(\varphi\hat{}^2/9r)^{1/2} > 1.645$. The probability of a type I error (false positive) with this test is approximately 5%. This test uses the same estimator of Z that formed the basis for sample size estimation described above.

The distributions of overall and progression-free survival will also be summarized using the method of Kaplan and Meier and compared among important subgroups using the logrank test. Differences in the frequency of objective response by treatment will be compared using the chi-square test. Multivariable and longitudinal analysis of tumor size and objective response will be conducted using generalized linear (mixed as appropriate) models with appropriate link functions.

7.1.6 **Pharmacokinetics/Pharmacodynamics/Biomarkers**

Exploratory objectives and endpoints are described in Sections 2.3 and 3.3. Briefly, for the proposed correlative studies, values obtained at either the best marrow response or at the time of progressive disease/end of treatment will be correlated with baseline values. However, because best marrow response and progressive disease may be suspected but not prospectively determined, bone marrow aspirate and peripheral blood samples will be collected from all patients prior to initiating protocol-indicated treatment, on Cycle 3 Day 1, on Cycle 7 Day 1, at time of suspected Progressive Disease and/or at the End of Treatment.

Samples for exploratory analyses will be collected and stored locally (short-term) according to a detailed laboratory manual. Samples will be shipped in batches from study sites to a central laboratory at Vanderbilt University Medical Center (i.e. the laboratory of the study chair, Dr. Michael Savona) for analysis and long-term storage. All studies will be performed in the central laboratory according to the detailed laboratory manual. Any leftover study tissue or blood samples may be stored for future research studies at the behest of the study sponsor as described in Section 4.1.2.18.

For exploratory studies, analyses may be performed on samples obtained from all patients or from a subset of patients. Studies to be performed on samples from all patients include:

- Mutational analysis using a panel of 37 genes frequently mutated in myeloid malignancy
- Mass cytometry.

Studies to be performed on samples from a subset of patients include.

- Genomic approaches such as RNAseq and Proseq
- Whole genome methylation studies.

Results from the studies and other appropriate technologies will be correlated with treatment response as defined in Section 11.3 for MDS or Section 11.4 for MDS/MPN.

7.1.7 Safety Analysis

Safety data will be summarized as requested by the sponsor investigator or data safety monitoring board using methods described in Section 7.1.5.

7.1.8 Stopping Rule

The following table describes the toxicity stopping boundary based on a Bayesian procedure. For this rule, only Grade ≥ 3 non-hematologic toxicity not including nausea amenable to antiemetics in 7 days or less, or Grade≥4 hematologic toxicity that does not resolve prior to starting the next cycle and occurs in patients with ≤ Grade 2 hematologic toxicity at baseline deemed by the investigator to be drug-related are considered for stopping. The beta distribution for acceptable toxicity was set at beta (3.55, 67.55), representing a 5% unacceptable toxicity rate in 71 patients. The prior distribution for the study toxicity was a beta (0.1,0.9), representing a 5% unacceptable toxicity in 2 patients. This weak prior is intentional so the observed outcomes quickly overwhelm the prior distribution if it is mis-specified. The stopping rule is based on satisfying the following probability statement. Stop the study for excessive toxicity if posterior probability of study toxicity being greater than acceptable toxicity (Pr(standard toxicity < experiment toxicity) > 0.95.) is greater than 95%.

Operating Characteristics.

1. If the true toxicity is 5%, the probability of stopping the study incorrectly for excessive toxicity by 15, 35, and 70 patients is 9.8%, 11.4% and 12.3%, respectively. The average number of patients treated is 63. 6, and average number of unacceptable toxicities is 3.2.

2. If the true toxicity is 20%, the probability of stopping early for excessive toxicity at 15, 35, and 70 patients is 67%, 88%, and 98%, respectively. The average number of patients treated is 15.4 and the average number of toxicities is 3.1.

Toxicity modelling was conducted using the Multc Lean Desktop: Version 2.1.0, Department of Biostatistics, MD Anderson Cancer Center.

To use this rule:

1. Find the number of patients enrolled in the left column. (The range is inclusive.)

2. The trial should be stopped if the number of toxicities is in the range of the right column. (The range is inclusive.)

Examples of when this stopping rule would apply would be if there were 4 or more unacceptable toxicities experienced in the first 16-24 patients or if 7 or more unacceptable toxicities were observed in the first 44-53 patients.

Note that if the trial should continue or stop regardless of the number of toxicities, this is indicated in the right-side column instead of a toxicity range. Note also that this full toxicity stopping boundary may include stopping conditions which are logically impossible to reach if the trial is conducted properly.

Table 7.1 Stopping Rule

# Patients enrolled (inclusive)	Stop the trial if Total # of Unacceptable Toxicities* (inclusive)
1	1
2-7	2-7
8-15	3-15
16-24	4-24
25-33	5-33
34-43	6-43
44-53	7-53
54-62	8-62
63-70	9-70
71	Always stop

*Unacceptable toxicity is defined as Grade ≥ 3 non-hematologic toxicity or Grade ≥ 4 hematologic toxicity that is deemed to be drug-related

8. ADVERSE EVENTS

Safety assessments will consist of monitoring and reporting AEs that are considered possibly, probably or definitely related to the investigational treatment (i.e. to azacitidine, pevonedistat, or the combination of azacitidine + pevonedistat). All SAEs, severe AEs (i.e. Grade ≥ 3), events of death, and any study-specific issues of concern will be monitored and reported, regardless of event attribution.

Adverse event collection and reporting is a routine part of every clinical trial. Each adverse event will be graded according to the NCI CTCAE, Version 4.03, dated June 14, 2010, currently locatable via the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

For events not listed in the CTCAE, severity will be designated as mild, moderate, severe, life threatening, or fatal which respectively correspond to Grades 1, 2, 3, 4, and 5 on the NCI CTCAE, with the following definitions:

- **Mild**: An event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate**: An event not resulting in disability or incapacity but which requires intervention;
- **Severe**: An event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening**: An event in which the patient was at risk of death at the time of the event;
- **Fatal**: An event that results in the death of the patient.

Information on all AEs, whether serious or not, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Reporting period: AEs experienced by participants will be collected and reported from initiation of investigational treatment (to also include events preceding initiation of study

treatment if an AE is at least possibly related to withholding medication prohibited by protocol, or a study procedure such as a biopsy), throughout the study, and within 30 days after the last dose of study medication. Participants who experience an AE related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Unless otherwise specified by protocol or a patient's study physician, asymptomatic abnormal laboratory values of Grade 1 or Grade 2 that do not trigger dose interruption or modification of protocol-indicated treatment will be deemed not clinically significant and are not required to be individually noted or recorded within the study data. Laboratory and vital sign abnormalities are to be recorded as AEs only if they are medically relevant as judged by the investigator (e.g. symptomatic, requiring corrective treatment, leading to dose modification or discontinuation of protocol-indicated treatment, and/or fulfilling a seriousness criterion). All SAEs regardless of Grade, severe AEs (i.e. Grade ≥ 3), and events of death will be recorded, regardless of event attribution.

Baseline disease-related signs and symptoms which are initially recorded as medical history, will subsequently be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

8.1 Definitions

8.1.1 Adverse Event

Adverse event means any untoward medical occurrence in a patient or subject administered a medicinal 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, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol imposed intervention, regardless of attribution.

An adverse event includes the following:

- Signs or symptoms that were not present or observed in the patient prior to the AE reporting period and that emerge during the protocol-specified AE reporting period (i.e. TEAEs).

- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures such as biopsy).

- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

- Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms, require treatment or further diagnostic tests, or lead to discontinuation or delay in treatment, or dose modification or if it represents a clinically significant change from the baseline as determined by the investigator.

Progressive disease will not be considered an adverse event.

8.1.2 **Adverse Drug Reaction**

An adverse drug reaction (ADR) is defined as an appreciably harmful or unpleasant reaction, resulting from the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.

As listed in the current product insert[32], the most common adverse reactions (>30%) associated with azacitidine by the SC route are: nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. The most common adverse reactions associated with azacitidine by the IV route also included petechiae, rigors, weakness and hypokalemia.

Azacitidine adverse reactions most frequently (>2%) resulting in clinical intervention (SC or IV Route) are:

- Discontinuation: leukopenia, thrombocytopenia, neutropenia.

- Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.

- Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

As listed in the current IB[22], ADRs associated with pevonedistat and considered expected for the purposes of regulatory reporting include the following, listed by preferred MedDRA (Medical Dictionary for Regulatory Activities) term:

- **Cardiac disorders:** Increased heart rate

- **Gastrointestinal disorders**: Diarrhea, Nausea, Vomiting

- **General disorders and administration site conditions**: Pyrexia

- **Investigations**: Liver function test abnormal

- **Musculoskeletal and connective tissue disorders**: Myalgia, Musculoskeletal pain.

These above mentioned ADRs are considered identified risks of pevonedistat. Medical concepts that are represented by the above preferred terms are treated as expected ADRs. If a reported adverse reaction represents added medical specificity, severity or duration, the adverse reaction may be considered unexpected.

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 1-4 increases in alanine aminotransferase and aspartate aminotransferase have been observed in patients receiving single-agent pevonedistat for relapsed and refractory AML. The patients experiencing these changes in laboratory values have been asymptomatic, and have been deemed both related and unrelated to pevonedistat treatment by investigators. 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.

A more detailed safety profile of azacitidine and pevonedistat are provided in the azacitidine product insert[32] and pevonedistat IB[22].

8.1.3 Serious Adverse Event (SAE)

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e. the AE actually causes or leads to death).
- It is life threatening (i.e. the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization, but not to include routine hospitalizations for neutropenic fevers that do not result in sepsis syndrome and/or ICU transfer.
- It results in persistent or significant disability/incapacity (i.e. the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator (e.g. may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above). 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, the event 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 (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a 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.

Events not considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.
- Respite care.

8.2 Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e. start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the investigational treatment (see following guidance), and actions taken. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

8.2.1 Expectedness

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the IB[22], the package insert[32], in published medical literature, in the protocol, or is included in the informed consent form as a potential risk.

An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the IB[22], the package insert[32], in

published medical literature, in the protocol, or is not included in the informed consent form as a potential risk.

8.2.2 Attribution

The investigator must attempt to determine if there exists reasonable possibility that an AE or SAE is related to the use of the investigational treatment. To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guidelines when determining if an AE or SAE is treatment-related:

- Treatment-Related: There is a reasonable causal relationship between the investigational treatment and the adverse event. There is a plausible temporal relationship between the onset of the AE and administration of the investigational treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational treatment; and/or the AE abates or resolves upon discontinuation of the investigational treatment or dose reduction and, if applicable, reappears upon re-challenge.

- Not Treatment-Related: There is no reasonable causal relationship between the investigational treatment administered and the adverse event. Evidence exists that the AE has an etiology other than the investigational treatment (e.g. pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational treatment.

Attribution of adverse events should be described as unrelated; or unlikely, possibly, probably, or definitely related to the investigational treatment:

Attribution	Description
Unrelated	AE *is clearly NOT related* to the intervention.
Unlikely	AE *is doubtfully related* to the intervention.
Possible	AE *may be related* to the intervention.
Probable	AE *is likely related* to the intervention.
Definite	AE *is clearly related* to the intervention.

For additional purpose of any applicable binary regulatory reporting, an event should be considered unrelated to study treatment when its attribution is felt by the investigator to be either unrelated or unlikely related to investigational treatment. Similarly, an event should be considered related to study treatment, when its attribution is felt to be either possibly, probably, or definitely related to investigational treatment.

8.3 Adverse Event Reporting Procedures

8.3.1 Specific Instructions for Recording Adverse Events

Adverse events which are serious must be reported to Takeda Oncology (or designee) from the first dose of protocol-indicated treatment (i.e. azacitidine or pevonedistat) up to and including 30 days after administration of the last dose of azacitidine or pevonedistat (whichever occurs last).

A pretreatment event is any untoward medical occurrence in a patient or subject who has a 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.

Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. 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.

All SAEs regardless of grade, severe adverse events (grade 3 or higher), and events of death of any patient during the course of the trial will be reported in the case report form, and the investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). With the exception of adverse events of special interest (see below), adverse events of Grade 1 or Grade 2 will not be reported in the case report form.

With the exception of adverse events of special interest (see below), asymptomatic abnormal laboratory values of Grade 1 or Grade 2 that do not trigger dose interruption or modification of protocol-indicated treatment will be deemed not clinically significant and are not required to be individually noted or recorded within the study data.

Laboratory and vital sign abnormalities are to be recorded as AEs only if they are medically relevant as judged by the investigator (e.g. symptomatic, requiring corrective treatment, leading to dose modification or discontinuation of protocol-indicated treatment, and/or fulfilling a seriousness criterion).

Adverse events of special interest that occur at grade 1 or higher will be recorded. Adverse events of special interest are: infection, AST/ALT increases, and bilirubin increases.

Any SAE that occurs at any time after completion of protocol-indicated treatment or after the designated follow-up period that the study chair and/or sub-investigator considers to be related to any study drug must be reported to Takeda Pharmacovigilance (or designee). 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 (e.g. surgery was performed earlier or later than planned).

All 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).

Since this is an investigator-initiated study, the Vanderbilt principal investigator, also referred to as the study chair, is responsible for reporting SAEs to any regulatory agency and to the study chair's EC or IRB.

Regardless of expectedness or causality, all SAEs must be reported in English to VICC coordinating center within 24 hours of the site becoming aware of the event. The VICC Multi-Institutional Coordinating Office will report all SAEs to Takeda Pharmacovigilance per the below outlined timelines:

- Fatal and life-threatening SAEs within 24 hours of the study chair's observation or awareness of the event
- All other serious (non-fatal/non-life threatening) events within 4 calendar days of the study chair's observation or awareness of the event

The SAE report must include at minimum:

- **Event term(s)**
- **Seriousness criteria**

- **Intensity of the event(s)**: Investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined using the NCI CTCAE version 4.03 as a guideline, whenever possible. The criteria are available online at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

- **Causality of the event(s)**: Investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Takeda Pharmacovigilance (or designee).

Because this is a multisite study, the study chair/Coordinating Center (i.e. Vanderbilt) is responsible to ensure that the SAE reports are sent to Takeda Pharmacovigilance (or designee) from all sites participating in the study.

Participating sites must report all SAEs to the study chair/Coordinating Center (i.e. Vanderbilt) so that the study chair can meet his/her foregoing reporting obligations to the required regulatory agencies and to Takeda Pharmacovigilance.

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

8.3.2 Diagnosis versus Signs and Symptoms

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. All adverse events will be captured on the appropriate study-specific CRFs.

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Adverse events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other

diagnostic procedures. 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 one comprehensive event.

8.3.3 Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study CRF.

8.3.4 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

8.3.5 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or

- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

8.3.6 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

8.3.6.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 4 months after the last dose of study drug. Pregnancy should be confirmed with a serum pregnancy test. The patient should permanently discontinue protocol-indicated treatment. If a woman suspects that she is pregnant while participating in this study, she must inform the investigator immediately and study treatment should be withheld until pregnancy is confirmed by aserum pregnancy test. If serum pregnancy test is positive, the patient should permanently discontinue protocol-indicated treatment.

The local investigator must complete the Pregnancy Form and submit it to the study chair/coordinating center ([redacted]) within 24 hours of the site becoming aware. The Coordinating Center will submit the completed Pregnancy Form to the Takeda Pharmacovigilance or designee (see Section 8.3.10).

The investigator or medical designee should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g. an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported using the Vanderbilt SAE form. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee may request this information from the study chair.

8.3.6.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the informed consent form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after completing treatment with azacitidine/pevonedistat. Male patients who received study treatment should not attempt to father a child until 4 months after stopping study treatment. A Pregnancy Form should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and faxed or emailed to the study chair ([redacted]). Attempts should be made to collect and report details of

the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner may be asked to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator or designee will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. An investigator or medical designee who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the local investigator must immediately notify the study chair / coordinating center, which must fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee immediately (see Section 8.3.10). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

8.3.7 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior azacitidine or pevonedistat exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

8.3.8 Serious Adverse Events

All serious adverse events, regardless of causality to study drug, will be reported to the principal investigator and/or the study coordinator at each institution, and also to the coordinating center.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 8.1.3) must be reported from the first dose of protocol-indicated treatment (i.e. azacitidine or pevonedistat) up to and including 30 days after administration of the last dose of azacitidine or pevonedistat (whichever occurs last) by the investigator to the coordinating center within 24 hours after the treating institution becomes aware of the event.

Serious Adverse Events should be reported to the coordinating center using the Vanderbilt Coordinating Center SAE form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to the Vanderbilt-Ingram Cancer Center (VICC) Multi-Institutional Coordinating Office 24 hours after the treating institution becomes aware of the event. SAEs must be recorded on the Vanderbilt Coordinating Center SAE form; pregnancies on a Pregnancy Form.

The SAE and Pregnancy forms will be provided to sites as part of a packet of supplemental forms.

Participating sites must complete the Vanderbilt Coordinating Center SAE forms, and submit via secure email transfer or via fax to:

Transmission of the SAE report should be confirmed by the site personnel submitting the report. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the VICC Multi-Institutional Coordinating Office as soon as it is available; these reports should also be submitted using the Vanderbilt SAE Form.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the local site's responsible IRB.

The coordinating center will disseminate information regarding serious adverse events to any participating sites within 5 days of review of the information by the Study chair (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e. possibly, probably, or definitely) to protocol-indicated treatment against the disease under study.

Vanderbilt University Medical Center acting as the Coordinating Center will be responsible for reporting of events to Takeda and the FDA as appropriate (outlined below).

Events should be reported to the FDA using a MedWatch form FDA 3500A (Mandatory Reporting Form for investigational agents). The FDA form can be found online, currently at http://www.fda.gov/safety/medwatch/howtoreport/default.htm and the Vanderbilt SAE form is part of the packet of supplemental forms.

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

8.3.9 **Institutional Review Board**

All adverse events and serious adverse events will be reported by each site to the local site's responsible IRB per its current institutional standards. If an adverse event requires modification to the informed consent or study protocol, these modifications will be provided to the IRB as soon as is possible, subsequent to consultation and agreement between the local investigator and the study chair.

8.3.10 **Takeda Oncology**

Vanderbilt University Medical Center acting as the Coordinating Center will be responsible for reporting to Takeda Oncology (or designee) any SAE that occurs during the SAE reporting period.

The Coordinating Center will report all SAEs, regardless of causality, to Takeda Pharmacovigilance (or designee), via email or facsimile to the following:

SAE Email Address: takedaoncocases@cognizant.com
SAE Facsimile Number: 1-800-963-6290

SAEs will be reported to Takeda Pharmacovigilance within the below outlined timelines:

- Fatal and life-threatening SAEs within 24 hours of the study chair's observation or awareness of the event
- All other serious (non-fatal/non-life threatening) events within 4 calendar days of the study chair's observation or awareness of the event

The study chair will ensure that all SAEs in the clinical database are appropriately reported to Takeda Oncology and any applicable health authority during the conduct of the study including periodic reconciliation.

8.3.11 **Food and Drug Administration (FDA)**

In this trial, unexpected adverse events believed to be possibly, probably or definitely related to pevonedistat, azacitidine, or the combination of pevonedistat + azacitidine will be reported to the FDA:

- via MedWatch (using the online form currently available at https://www.accessdata.fda.gov/scripts/medwatch/);
- by telephone 1-800-FDA-1088;
- or by fax 1-800-FDA-0178 (using the form currently available at http://www.fda.gov/medwatch/report/hcp.htm).

For all participating sites, the coordinating center will be responsible for correspondence with the FDA regarding adverse events.

8.3.12 **Additional Reporting Requirements for IND**

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report

The Study chair is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed to be possibly, probably or definitely related to the use of azacitidine or pevonedistat. An unexpected AE is one that varies in nature, intensity or frequency from information provided in the current adverse event list, the IB[22], the package insert[32], in published medical literature, in the protocol, or is not included in the informed consent document as a potential risk of azacitidine or pevonedistat. Such reports are to be telephoned or faxed to the FDA within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Study chair is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of pevonedistat or azacitidine. An unexpected AE is one that varies in nature, intensity or frequency from information provided in the current adverse event list, the IB[22], the package insert[32], in published medical literature, in the protocol, or is

not included in the informed consent document as a potential risk of azacitidine or pevonedistat.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with analysis of similar events are to be submitted to the FDA and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g. summary letter). Contact Information for IND Safety Reports:

FDA fax number for IND safety reports: 1-800-332-0178.

8.4 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 Takeda (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

For Product Complaints, call
Phone 1-844-ONC-TKDA (1-844-662-8532)
Email: GlobalOncologyMedinfo@takeda.com

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 Takeda Pharmacovigilance (refer to Section 8.3.10).

9. ADMINISTRATIVE AND REGULATORY REQUIREMENTS

This is an investigator-initiated study. The Study Chair, Michael R. Savona, M.D., (who may also be referred to as the sponsor -investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the Study Chair include both those of a sponsor and those of an investigator.

9.1 Data Safety and Monitoring

9.1.1 Data Management and Reporting

Participating institutions will collaborate with Vanderbilt for patient accrual. Data will be collected using a centralized eCRF called Synalytics.

Synalytics is a Vanderbilt Center for Quantitative Sciences (CQS) open-source software system for rapid development and implementation of secure, password-protected, SSL-encrypted, 21CRF11-ready, web-based electronic data capture (EDC) systems to meet a wide range of clinical and non-clinical biomedical research needs.

The central engine of the Synalytics software system is the Codex API, an application programming interface custom-developed by the Vanderbilt CQS, using the node.js programming language. The Codex API is flexible for interaction with other software systems. For its central role in EDC build-out, Codex reads and interprets a schema file describing the data to be captured, and automatically creates a corresponding data capture application. This simple application may then be further customized to apply complex data validations, automated notifications and alerts, or other features as applicable to project-specific needs (please see list below for features available). Data capture is in MongoDB, and the graphical user interface (GUI) is rendered using angular.js. A Synalytics EDC can:

- Model complex longitudinal data, including data with an open-ended number of repeated observations, as well as nested longitudinal data with n-dimensional nesting.

- Apply intra- as well as inter-variable validations at the point of data entry, including dynamic validation of the value of a given variable against one or more other user-entered variables, for logical or clinical consistency or other custom flag.

- Apply branching logic in complex ways to minimize need for redundant or non-applicable data entry; for example, application of branching logic across eCRFs and study time points; branching logic driven by interaction of study time point with other patient covariates; branching logic that dictates conditional eCRF attachment to study time points and/or allows for flexible eCRF attachment.

- Implement a comprehensive data monitoring / query resolution workflow for manual data query and verification by a data monitoring user, as well as automated query

functionalities, such as auto-query of lab values that lie outside a selected reference range.

- Implement auto-population of variable values, including simple calculated fields as well as more complicated auto-population functions such as auto-population driven by branching logic, or auto-population of values from a parent eCRF to a child eCRF, for entry of follow-up data or other data types that may need to reference the parent data.

- Capture comprehensive audit metrics, including user, action, and specific data change made.

- Implement alerts and notifications, whether in real-time (i.e., submission of a particular form or particular data point triggers an instantaneous email notification), or with delayed job scheduling (i.e., email prompts that continue to escalate until action is taken; email prompts for longitudinal follow-up, such as emails automatically scheduled for 3, 6, and 12-month follow-up after baseline data entry).

- Implement any number of levels of tiered user permissions, with password-protected user accounts for database access, as well as 'state machines' to provide fundamentally different EDC navigation and use experience for different user types (e.g., patient users, for patient-reported outcomes, vs. research team users).

- Implement automated data reporting pipelines, for example, preparation of tables, summary statistics, and other reporting metrics for repeated needs such as data safety and monitoring board (DSMB) reporting.

Specified members at each participating site will submit all pertinent regulatory documents to the Coordinating Center, who will store it in a secure location.

The Principal Investigator or designee at each site will inform the coordinating center as defined in any Safety and Data Exchange Agreement of any serious adverse event, and will also inform the site's local IRB in accordance with each institution's IRB policy. The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the treating investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs, as detailed in the protocol. If any problem appropriate for review is identified related to the conduct of this research, the VICC Data

Safety and Monitoring Committee (DSMC) will be formally asked to review the study and the situation that required DSMC intervention.

9.1.2 **Monitoring**

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

VICC Multi-Institutional Coordinating Center

The trial additionally will be monitored by the VICC Multi-Institutional Coordinating Center. The actual frequency of monitoring will depend on the enrollment rate and performance of the site. Monitoring will be conducted through onsite and remote monitoring, teleconferences with the Investigator and site staff, and appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions, and to ensure the quality and integrity of the data.

During scheduled monitoring visits, investigators and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests, provide required regulatory documents, and respond to any other trial-related inquiries of the monitor.

In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

9.1.3 Data Handling and Record Keeping

An eCRF is required and must be completed for each included participant. The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt.

To enable evaluations and/or audits from health authorities and Vanderbilt, each site investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed online. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

9.2 Regulatory Considerations

9.2.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to IRB per current institutional standards.

The trial will not be initiated until there is approval by the local IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial. The IRB should be duly constituted according to local regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly.

Any changes to the protocol will be made in the form of a written amendment and must be approved by the study chair and the local IRB prior to local implementation. All amendments will also be submitted as necessary to the FDA by the study chair (or designee).

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB; and the study chair (or designee), who will communicate as appropriate with the FDA.

The study chair (or designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

9.2.2 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent form (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

9.2.3 Ethics and Good Clinical Practice

This study will be carried out in compliance with the protocol and Good Clinical Practice (GCP), as described within:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996[39]
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described within the above and thereby to adhere to the principles of Good Clinical Practice with which the above conform.

9.2.4 Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier, which will be used on all CRFs and any other material submitted to regulatory authorities. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial.

9.2.5 Study Termination

The study chair reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns
- Decision by suppliers to modify or discontinue the availability, development or manufacture of pevonedistat and/or azacitidine.
- A request to discontinue the study by the IRB or FDA.

The study chair will promptly notify investigators, the IRB and FDA if the study is terminated for any reason.

9.3 Multi-Center Guidelines

9.3.1 Pre-Study Documentation

Prior to initiating the trial, the investigator will provide to the Coordinating Center essential documents, including but not limited to:

- A signed FDA Form 1572
- A current curriculum vitae for the Principal Investigator and each sub-investigator listed on the FDA Form 1572
- A copy of the current medical license for each investigator (as applicable)
- A letter from the IRB stipulating approval of the protocol, the informed consent form and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- A copy of the IRB-approved informed consent form
- The current IRB membership list for the reviewing IRB
- A completed financial disclosure form for the principal investigator and all sub-investigators
- Current laboratory certification for the reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory.

9.3.2 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the IRB per the current institutional standards of each participating center.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to local implementation.

The study chair (or designee) is responsible for the coordination and development of all protocol amendments. Once approved by the study chair, Vanderbilt will disseminate this information to the participating centers.

9.3.3 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the coordinating center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The coordinating center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the coordinating center.

The requirements for data management, submissions, and monitoring are outlined below. The participating sites will submit all the research related information (source documents and research records – IRB approval documents, patient registration list, CRF info, toxicity assessments, tumor measurements / responses, etc.) to the Coordinating Center, for processing at the appropriate time points: prior to study initiation, when patients are enrolled, and as requested during study duration. Personnel from the VICC Clinical Trial Shared Resource (CTSR) will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

9.3.4 Records Retention

United States (US) FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the US FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The coordinating center will inform the investigator at each site at such time that the records may be destroyed.

9.3.5 Publication

It is understood that any manuscript or releases resulting from the collaborative research must be approved by the Study Chair and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation.

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11. APPENDICES

11.1 Appendix 1: WHO Classification of MDS and MDS/MPN[10]

Myelodysplastic syndrome (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*–negative
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable

Source: Arber, D. A. et al. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood 127, 2391-405, (2016)[10].

11.2 Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

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 (e.g., light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, 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[40].

11.3 Appendix 3: Response Criteria for MDS

The modified recommendations of the International Working Group (IWG) for Response Criteria[41] for altering natural history of MDS will be used for assessment of disease response. Investigators are encouraged to consult the reference for more detailed explanation of response criteria. Note: per IWG recommendations, responses must last at least 4 weeks. For the purposes of this study, if criteria are met for CR, Marrow CR, PR or stable disease (SD) at a single time point, the response will be recorded as such, but will be considered unconfirmed until subsequent analysis can be performed.

Complete remission (CR):

- Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines. Persistent dysplasia will be noted.
- Peripheral blood:

  Hemoglobin ≥ 11 g/dL
  Platelets ≥ 100 x 10^9/L
  Neutrophils ≥ 1.0 x 10^9/L
  Blasts 0%

Marrow CR:

- Bone marrow: ≤5% myeloblasts and decreased by ≥50% over pretreatment
- Peripheral blood: Hematologic improvements will be noted separately, in addition to marrow CR

Partial Remission (PR):

- Bone marrow: >5% myeloblasts, but decreased by ≥50% over pretreatment
- Peripheral blood:

  Hemoglobin ≥ 11 g/dL
  Platelets ≥ 100 x 10^9/L
  Neutrophils ≥ 1.0 x 10^9/L
  Blasts 0%

Stable disease (SD):

- Failure to achieve at least PR, but no evidence of progression for > 8weeks

Progressive Disease (PD):

- Bone marrow: > 50% increase in bone marrow blasts from baseline value
- Peripheral blood: ≥ 50% decrease from maximal response in neutrophils or platelets
    - Reduction in Hemoglobin ≥ 2 g/dL
    - Transfusion dependence

Cytogenetic Response:

- Complete: Disappearance of previously demonstrated chromosomal abnormality without appearance of new ones
- Partial: At least 50% reduction of previously demonstrated chromosomal abnormality

Hematologic Improvement (HI):

- **Erythroid response (pretreatment Hemoglobin < 11 g/dL)**
    - Hemoglobin increase by ≥ 1.5 g/dL
    - Reduction in the number of units of RBC transfusions by an absolute number of ≥4 RBC units/8 weeks compared with the number of units transfused in the 8 week period prior to treatment initiation (only RBC transfusions given for hemoglobin ≤ 9 g/dL should be counted in the response evaluation)
- **Platelet response (pretreatment platelet < 100 x 10^9/L)**
    - Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9 /L platelets
    - Increase from < 20 x 10^9/L to >20 x 10^9/L and by at least 100%
- **Neutrophil response (pretreatment ANC < 1.0 x 10^9/L)**
    - At least 100% increase and an absolute increase > 0.5 x 10^9/L
- **Progression or relapse after HI**
    - At least one of the following, after meeting criteria for HI above:
        - At least 50% decrease from maximum response levels in neutrophils or platelets
        - Reduction in Hemoglobin by ≥ 1.5 g/dL
        - Transfusion dependence

Investigators should note that some patients may benefit from continued treatment even though their bone marrow blast counts may fluctuate. 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 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.

Therefore, clinical benefit to a patient should be considered before discontinuing treatment in patients who meet the criteria for progressive disease based only on bone marrow blast counts. After discussion and agreement between the investigator and study chair, patients with increase in bone marrow blasts (but blast count < 20%) may be allowed to remain on study if they are receiving clinical benefit.

11.4 Appendix 4: Modified Response Criteria for MDS/MPN Overlap Syndromes

The International Consortium of clinical experts in MDS/MPN devised uniform response criteria as well as criteria for disease progression in MDS/MPN overlap syndromes based on three independent academic MDS/MPN workshops (Marsh 2013, December 2013 and June 2014)[38]. Responses in MDS/MPN overlap syndromes will be assessed according to the Uniform Response Criteria with two modifications. First, in the original response criteria, complete remission and optimal marrow response both require return of the marrow to normocellularity Recognizing that the definition of normocellularity is estimated for each patient based on their age and that its evaluation is both subjective and imprecise, the return to normocellularity shall not be a strict requirement for assessing bone marrow response in MDS/MPN subjects. In order to achieve complete remission or optimal marrow response, the bone marrow examination must show ≤ 5% myeloblasts (including monocytic blast equivalents in the case of CMML) with normal maturation of all cell lines and absent or only mild reticulin fibrosis. Finally, in the original criteria, there is no response category for patients who do not meet criteria for response but who also do not meet criteria for disease progression. Provision for "Stable Disease" has been added.

Investigators are encouraged to consult the reference for more detailed explanation of response criteria. Note: It is recommended that a complete CR be confirmed by a minimum of 2 bone marrow evaluations at least 8 weeks apart documenting improvement in fibrosis and that peripheral blood improvements be maintained over at least 8 weeks to qualify for response. For the purpose of this study, if criteria are met for response (CR, PR, marrow response or clinical benefit) at a single time point, the response will be recorded as such, but will be considered unconfirmed until subsequent analyses can be performed.

Complete remission (CR): (all of the following improvements must be met)

- Bone marrow: ≤ 5% myeloblasts (including monocytic blast equivalents in the case of CMML) with normal maturation of all cell lines. Persistent dysplasia may be noted.
- Myelofibrosis absent or equal to "mild reticulin fibrosis" or ≤ Grade 1 fibrosis
- Peripheral blood:
    - WBC ≤ 10 x 10^9/L but ≥ 1.5 x 10^9 /L
    - Hemoglobin ≥ 11 g/dL
    - Platelets ≥ 100 x 10^9/L but ≤ 450 x 10^9/L
    - Neutrophils ≥ 1.0 x 10^9/L and precursors reduced to ≤ 2%
    - Monocytes ≤ 1 x 10^9/L

  - Blasts 0%
- Extramedullary disease: Complete resolution of extramedullary disease present before therapy (e.g. cutaneous disease, disease-related serous effusions and palpable splenomegaly)

Complete cytogenetic remission:

- Resolution of previously present chromosomal abnormality (known to be associated with MDS, MPN or MDS/MPN) as seen on karyotyping with minimal of 20 metaphases or by fluorescence *in situ* hybridization (FISH)

Marrow response:

- Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices and/or extramedullary disease
- Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity without normalization of peripheral blood indices and/or extramedullary disease, OR reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 months apart

Partial Remission:

- Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of marrow cellularity *except* in cases of MDS/MPN with ≤ 5% bone marrow blasts at baseline

Clinical benefit:

A subject who does not meet criteria for complete or partial remission or progressive disease, may be assessed for clinical benefit. Clinical benefit will be assessed independently of marrow response. As an example, a subject may have an optimal marrow response and spleen response but not have normalization of peripheral blood indices. Alternatively, patients who do not meet criteria for marrow response but who have normalization in peripheral blood indices and improvement in splenomegaly may be assessed as having clinical benefit with erythroid and spleen responses.) Subjects who achieve clinical benefit meet one or more of the following criteria:

- **Erythroid response**
  - Hemoglobin increase by ≥ 2.0 g/dL
  - Transfusion independence (TI) for ≥ 8 weeks for patients requiring ≥ 4 units of RBC transfusions in the 8 week period prior to treatment. TI is defined as requirement of <4 units of RBCs over an 8 week period (only

RBC transfusions given for hemoglobin ≤ 8.5 g/dL should be counted in the TI response evaluation)

- **Platelet response**
  - Transfusion independence when previously requiring ≥ 4 platelet transfusions in an 8 week period. TI is defined as requirement of <4 units of platelets over an 8 week period.
  - For pretreatment platelet count ≤ 20 x 10^9 /L: increase of at least 100% over pretreatment platelet count to an absolute count > 20 x 10^9 /L
  - For pretreatment platelet count >20 x 10^9 /L but ≤ 100 x 10^9 /L: absolute increase of ≥ 30 x 10^9 /L
- **Neutrophil response**
  - For pretreatment ANC ≤ 0.5 x 10^9 /L : at least 100% increase and an absolute increase ≥ 0.5 x 10^9/L
  - For pretreatment ANC > 0.5 x 10^9 /L but ≤ 1.0 x 10^9 /L: at least 50% increase and an absolute increase ≥ 0.5 x 10^9/L
- **Spleen response**
  - Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
- **Symptom response**
  - Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS. Subjects scoring <20 on the MPN-SAF were not considered eligible for measuring symptom response.

Stable Disease:

Failure to achieve at least a partial response with no clinical benefit but also no evidence of disease progression (see criteria in Table **11-1** below.)

Progressive Disease:

Assessment of disease progression will follow criteria proposed by the International Consortium of clinical experts on MDS/MPN, as outlined in Table 11- below:

Table 11-1: Criteria for Measurement of Disease Progression in Adult MDS/MPN

Major Criteria	Minor Criteria
Increase in bone marrow blast count by at least 50% AND: • From < 5% blasts to > 5% blasts, or • From 5-10% blasts to > 10% blasts, or • From 10-20% blasts to > 20% blasts*	Transfusion dependence Defined as requiring ≥ 2 units of RBC transfusions in the past month for a hemoglobin < 8.5 g/dL not associated with clinically overt bleeding
Evidence of cytogenetic evolution • Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or karyotype • Increase in cytogenetic burden of disease by ≥ 50% in partial cytogenetic remission via FISH or karyotype	Worsening cytopenias • Defined as ≥ 50% decrease from maximal remission/response in granulocytes or platelets • Reduction in hemoglobin by ≥ 1.5 g/dL from best response or from baseline as noted on CBC
New extramedullary disease • Progressive splenomegaly defined as o Appearance of previously absent splenomegaly that is palpable at >5 cm below the left costal margin, or o A minimum 100% increase in palpable distance for baseline splenomegaly 5-10 cm, or o A minimum 50% increase in palpable distance for baseline splenomegaly of > 10 cm • Outside the spleen o Hepatomegaly o Granulocytic sarcoma o Skin lesions	Increasing symptoms • As noted by increase of ≥50% as per the MPN-SAF Total Symptom Score† Evidence of clonal evolution (molecular) • Defined as identification of new abnormalities using single nucleotide polymorphism arrays or sequencing or a clearly significant increase in mutational burden of a previously detected abnormality
Progressive Disease defined as meeting: • **2 major criteria, or** • **1 major and 2 minor criteria, or** • **3 minor criteria**	

* Increase in myeloblasts to >20% is considered progression to acute myeloid leukemia
†MPN-SAF Total Symptom Score was developed for myeloproliferative neoplasm symptom assessment.

11.5 Appendix 5: Cockcroft-Gault Formula

The Cockcroft-Gault formula may be used for estimated creatinine clearance rate (eC_{CR}). The use of on-line calculators or formulas, which are institution standards for eC_{CR} and which differ slightly may also be used. The calculations and results must be filed in the patient's chart.

When serum creatinine is measured in mg/dL:

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass (in kilograms)} \cdot [0.85 \, if \ Female]}{72 \cdot \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L:

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass (in kilograms)} \cdot \text{Constant}}{\text{Serum Creatinine (in µmol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

11.6 Appendix 6: Acceptable Contraception

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 potential and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal – i.e. amenorrheic without an alternative medical cause – for at least 1 year prior to the date of signed informed consent (note: postmenopausal status in females under 55 years of age should be confirmed with a serum FSH level within laboratory reference range for postmenopausal women), or
- Surgically sterile (i.e. patient has had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy), or
- If of childbearing potential, female patient agrees to practice 2 methods of effective contraception (see **Error! Reference source not found.**) at the same time, from the time of signing the informed consent through 4 months after patient's last dose of pevonedistat or azacitidine (whichever dose occurs last), or
- Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient.

Male patients, even if surgically sterilized (i.e. status post-vasectomy) who have female partners of childbearing potential must agree to 1 of the following:

- Practice effective barrier contraception (see **Error! Reference source not found.**) from the time of signing the informed consent through 4 months after patient's last dose of pevonedistat or azacitidine (whichever dose occurs last), or
- Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient.

A study physician or clinical designee shall counsel female patients of childbearing potential and male patients who have female partners of childbearing potential, regarding the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the use of acceptable contraception.

Table 11-2: Effective Methods of Contraception

Barrier Methods	Intrauterine Device Methods	Hormonal Methods	Surgical Methods
• Male or female condom plus spermicide • Cervical cap plus spermicide • Diaphragm plus spermicide	• Copper T (e.g. Paragard®) • Levonorgestrel-releasing intrauterine system (e.g. Mirena®) – also considered a hormonal method	• Implants • Hormone shot or injection • Combined pill (estrogen + progestin) • Minipill (progestin only) • Patch	• Bilateral tubal ligation • Hysterectomy • Bilateral oophorectomy

True abstinence, defined as complete avoidance of heterosexual intercourse, when consistent with the patient's preferred and established lifestyle, is an acceptable form of contraception for purposes of the study.

Periodic abstinence (e.g. calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable forms of contraception in this study.

In the event the patient chooses to forego true abstinence, acceptable methods of contraception must be discussed with the study physician or clinical designee.

11.7 Appendix 7: Excluded CYP3A Inducers

Based on study C15011, use of moderate and strong CYP3A inhibitors is permitted during pevonedistat therapy. Clinically significant metabolic CYP3A inducers listed in Table 11-3 should be avoided during pevonedistat therapy, however.

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

Table 11-3: *In Vivo* Clinically Significant Inducers of CYP3A

STRONG inducers ≥ 80% decrease in AUC	**MODERATE inducers** 50-80% decrease in AUC
Carbamazepine	Bosentan
Phenytoin	Efavirenz
Phenobarbital	Modafinil
Primidone	Nafcillin
Rifabutin	
Rifampin	
Rifapentine	
St. John's Wort	

Abbreviations:
AUC = area under the plasma concentration versus time curve;
CYP = cytochrome P450.

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