Title: A Phase 3, Randomized, Controlled, Open-label, Clinical Study of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine as First-Line Treatment for Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Low-Blast Acute Myelogenous Leukemia

NCT Number: NCT03268954

Protocol Approve Date: 21 September 2021

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

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

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

PROTOCOL

A Phase 3, Randomized, Controlled, Open-label, Clinical Study of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine as First-Line Treatment for Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Low-Blast Acute Myelogenous Leukemia

Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine as First-Line Treatment for Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Low-Blast Acute Myelogenous Leukemia

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

Study Number: Pevonedistat-3001

IND Number: 78,427 **EudraCT Number:** 2017-000318-40

Compound: Pevonedistat (TAK-924/MLN4924)

Date: 21 September 2021 **Amendment Number:** 14

Date	Amendment Number	Amendment Type	Region
03 August 2017	Initial Protocol	Not applicable	Global
05 December 2017	01	Substantial	United Kingdom
03 January 2018	02	Substantial	France
17 January 2018	03	Substantial	Germany
20 March 2018	04	Substantial	United Kingdom
17 August 2018	05	Substantial	Global
09 October 2018	06	Substantial	United Kingdom
31 March 2020	07	Substantial	Global
13 April 2020	08	Substantial	United Kingdom
24 July 2020	09	Substantial	China
29 September 2020	10	Substantial	Global
29 September 2020	11	Substantial	United Kingdom
26 March 2021	12	Substantial	Global
26 May 2021	13	Substantial	Global
21 September 2021	14	Substantial	Global

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

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

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

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

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

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

PPD

1.3 Protocol Amendment 14 Summary of Changes

Rationale for Amendment 14

This section describes the changes to the protocol incorporating Amendment 14. The primary reason for this amendment is to update the name of the legal entity to Takeda Development Center Americas, Inc. and to update its address.

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

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

Changes in Amendment 14

1. Updated the name of the legal entity to Takeda Development Center Americas, Inc., 95 Hayden Avenue, Lexington, MA 02421.

INVESTIGATOR AGREEMENT

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

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

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** Pevonedistat (TAK-924/MLN4924)	
Title of Protocol: A Phase 3, Randomized, Controlled, Open-label, Clinical Study of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine as First-Line Treatment for Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Low-Blast Acute Myelogenous Leukemia	**IND No.:** 78,427	**EudraCT No.:** 2017-000318-40
Study Number: Pevonedistat-3001	**Phase:** 3	

Study Design:

General eligibility may be assessed before the formal Screening period if it is part of standard clinical practice. However, formal screening will occur during the Screening period, which may last up to 28 days before randomization. The sponsor's project clinician (or designee) will confirm patient eligibility before randomization by the investigator.

Once enrolled, patients with myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), or low-blast acute myelogenous leukemia (AML) will be randomized at a 1:1 ratio to receive study drug (either single-agent azacitidine or the combination of pevonedistat and azacitidine) in 28-day treatment cycles. All patients will be stratified into 4 categories: low-blast AML, Revised International Prognostic Scoring System (IPSS-R) risk groups of very high, high, or intermediate for MDS or CMML [1]. Note that patients with higher-risk MDS (HR MDS) or CMML indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points, ie, intermediate, for determining overall Prognostic Risk Category/Score. Modifications to the dose and schedule may be allowed.

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

Patients will attend the End-of-Treatment (EOT) visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner.

Following the EOT visit, patients with HR MDS or CMML will enter event-free survival (EFS) follow-up, if their disease has not transformed to AML. Patients will have monthly assessments to include physical exam, clinical blood tests, health-related quality of life (HRQOL) assessments, hospitalization assessment, and disease assessment. Patients who discontinue study treatment without evidence of progression (ie, PD or transformation to AML) will have a bone marrow aspirate and hematology tests (see Table 9.d), at time of suspected progression and at the time of suspected transformation to AML if this event occurs later (specimens sent to central laboratory). Patients who discontinue treatment while in CR or partial remission (PR) will also have a bone marrow aspirate and hematology tests done at the time of suspected relapse (specimens sent to central laboratory). Patients will continue monthly EFS follow-up study visits until their disease transforms to AML. Patients who have started subsequent therapy will have EFS follow-up but will not be required to have monthly visits; at the time of suspected transformation to AML, they will have a bone marrow aspirate and hematology tests (specimen sent to central laboratory).

Following the EOT visit, patients with low-blast AML will enter response follow-up, if they have no evidence of PD and they have not started subsequent therapy. Patients will have monthly assessments to include physical exam, clinical blood tests, HRQOL assessments, hospitalization assessment, and disease assessment. Patients who

discontinue study treatment while not in CR and without evidence of PD will have a bone marrow aspirate and hematology tests done at the time of suspected PD (specimen sent to central laboratory). Patients who discontinue treatment while in CR will also have a bone marrow aspirate done at the time of suspected relapse (specimen sent to central laboratory). Patients will continue monthly response follow-up visits, until they relapse from CR or meet the criteria for PD.

Following the EFS and response follow-up visits, patients with HR MDS or CMML who discontinue study treatment because of transformation to AML, or patients with low-blast AML who discontinue study treatment because of PD, will enter overall survival (OS) follow-up and will be contacted every 3 months until death to document subsequent therapies and survival status.

Disease response assessments for all HR MDS and CMML patients will be based on the Modified International Working Group (IWG) response criteria for MDS [2]. Disease response assessments for patients with low-blast AML will be based on the Revised Recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [3]. Formal disease assessments for study endpoints will be determined based on local bone marrow aspirate blast counts (blast counts from the bone biopsy may be used in the event the aspirate sample is inadequate and a biopsy was done), clinical laboratory evaluations performed at a central laboratory (local laboratory results may be used for time-sensitive clinical decisions), and local transfusion data.

Inpatient hospital admissions related to HR MDS or CMML, or low-blast AML, as well as transfusion independence, will be monitored as secondary efficacy endpoints. Red blood cell (RBC) and platelet transfusion independence requires that the patient receive no RBC or platelet transfusions, respectively, for a period of at least 8 weeks during the time period from the first dose of study drug administration through 30 days after the last dose of any study drug. Treatment-emergent resistance also will be monitored.

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

Bone marrow aspirates and blood will be obtained at Screening and at additional time points for assessing response and/or for translational research purposes. Samples will be collected and analyzed (at a central laboratory) from patients in both treatment arms. Bone marrow aspirates and blood collected at Screening will be used to analyze tumor cytogenetics, baseline somatic mutations, and other molecular characteristics such as gene expression profile and epigenetic status. Bone marrow aspirates and blood collected at the specified time points during treatment and/or at relapse will be used to evaluate depth and duration of response by following parameters such as residual tumor cells, residual mutation load, and changes in epigenetic modifications. Such analysis will also be used to identify treatment-emergent mutations. Developing potential biomarkers of pevonedistat-mediated activity may require analysis of the data from this study in combination with data from other clinical studies of pevonedistat.

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

Adverse events and Eastern Cooperative Oncology Group (ECOG) performance status (PS) will be assessed, and electrocardiograms, clinical laboratory values, and vital signs will be obtained, to evaluate the safety and tolerability of the study drug treatments. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, effective date 14 June 2010 [4].

Patient-reported outcomes (PROs) will be evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), version 3.0 and EuroQoL 5 dimensions 5 levels (a quality of life questionnaire of the "EuroQoL Group Association" that was expanded to a 5-level instrument) (EQ-5D-5L) questionnaires.

Primary Objective:

- To determine whether the combination of pevonedistat and azacitidine improves EFS when compared with single-agent azacitidine. (An event is defined as death or transformation to AML in patients with MDS or CMML, whichever occurs first, and is defined as death in patients with low-blast AML.)

Key Secondary Objective:

- To determine whether the combination of pevonedistat and azacitidine improves OS when compared with single-agent azacitidine.

Other Secondary Objectives:

- To determine whether the combination of pevonedistat and azacitidine improves 6-month and 1-year survival rates when compared with single-agent azacitidine.
- To determine in patients with HR MDS, patients with HR CMML, and patients with HR MDS/CMML whether the combination of pevonedistat and azacitidine delays time to AML transformation when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves the rate of CR (CR in patients with HR MDS or CMML, or low-blast AML), CR+complete remission with incomplete blood count recovery (CRi) in patients with low-blast AML, CR+marrow CR (in patients with HR MDS or CMML), CR+PR+hematologic improvement (HI) (in patients with HR MDS or CMML), CR+marrow CR+PR (in patients with HR MDS or CMML), CR+marrow CR+PR+HI (in patients with HR MDS or CMML), overall response, overall response by Cycle 6, and overall response 2. Overall response in patients with HR MDS or CMML is defined as CR+PR; overall response in patients with low-blast AML is defined as CR+CRi+PR. Overall response 2 in patients with HR MDS or CMML is defined as CR+PR+HI; overall response 2 in patients with low-blast AML is defined as CR+CRi+PR.
- To determine whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves duration of CR (CR for HR MDS or CMML, or low-blast AML), CR+CRi for low-blast AML, overall response (CR+PR for HR MDS or CMML, CR+CRi+PR for low-blast AML), and overall response 2 (CR+PR+HI for HR MDS or CMML, CR+CRi+PR for low-blast AML).
- To determine whether the combination of pevonedistat and azacitidine improves rate of transfusion independence when compared with single-agent azacitidine. RBC and platelet transfusion independence requires that the patient receive no RBC or platelet transfusions for a period of at least 8 weeks during the time period from the first dose of study drug administration through 30 days after the last dose of any study drug.
- To determine whether the combination of pevonedistat and azacitidine increases the duration of RBC transfusion independence, platelet transfusion independence, or platelet and RBC transfusion independence, when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine improves time to first CR or PR (for HR MDS or CMML, or low-blast AML) and to first CR or CRi (for low-blast AML) when compared with single-agent azacitidine.
- To determine in patients with HR MDS, patients with HR MDS/CMML, and patients with HR CMML whether the combination of pevonedistat and azacitidine improves rates of HI when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine does not increase inpatient hospital admission(s) related to HR MDS, CMML, or low-blast AML when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine delays time to PD, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine maintains overall health status/quality of life and fatigue domain scores as measured by the PRO instrument EORTC QLQ-C30 when compared with single-agent azacitidine.
- To collect plasma concentration-time data for pevonedistat to contribute to future population PK analyses of pevonedistat.

- To compare ORR, EFS, and OS in patients who have *TP53* mutations, 17p deletions, and/or are determined to be in an adverse cytogenetic risk group at Baseline, across treatment arms.

Subject Population: Male or female patients aged 18 years or older with HR MDS or CMML, or low-blast AML.

Number of Subjects:	**Number of Sites:**
Estimated total: approximately 450 patients (randomized in a 1:1 ratio)	Estimated total: approximately 120 study centers globally
Dose Level(s): 28-day treatment cycles *Single-agent arm*: Azacitidine (75 mg/m^2 [intravenous (IV) or subcutaneous (SC)]) on Days 1 through 5, Day 8, and Day 9 *Combination arm*: Pevonedistat (20 mg/m^2 via 60 (±10)-minute infusion) on Days 1, 3, and 5 PLUS Azacitidine (75 mg/m^2 [IV or SC]) on Days 1 through 5, Day 8, and Day 9	**Route of Administration:** Pevonedistat: IV Azacitidine: IV or SC (per investigator's choice)
Duration of Treatment: Patients, including those who achieve a CR, may receive study treatment until they experience unacceptable toxicity, relapse, transformation to AML (for patients with HR MDS or CMML), or PD (for patients with low-blast AML), the sponsor terminates the study, or discontinuation due to other reasons. A minimum of 6 cycles of treatment is strongly encouraged.	**Period of Evaluation:** Up to approximately 6 years

Main Criteria for Inclusion:

- Morphologically confirmed diagnosis of MDS or nonproliferative CMML (ie, with white blood cell count <13,000/μL) or low-blast AML based on 1 of the following:

  French-American-British Classifications [5]:

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

  OR

  World Health Organization (WHO) Classifications [6]:

  – Refractory anemia with excess blasts-1 (RAEB-1), defined as having 5% to 9% myeloblasts in the bone marrow).
  – Refractory anemia with excess blasts-2 (RAEB-2), defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood).
  – Chronic myelomonocytic leukemia-2 (CMML-2), defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood.
  – Chronic myelomonocytic leukemia-1 (although CMML-1 is defined as having <10% myeloblasts in the bone marrow and/or <5% blasts in the blood, these patients may enroll only if bone marrow blasts are ≥5%).
  – WHO-defined AML with 20% to 30% myeloblasts in the bone marrow (defined in this protocol as

low-blast AML) and <30% myeloblasts in peripheral blood who are deemed by the investigator to be appropriate for azacitidine-based therapy.

- All patients with MDS or CMML must also have one of the following Prognostic Risk Categories, based on the IPSS-R [1]:
  - Very high (>6 points).
  - High (>4.5-6 points).
  - Intermediate (>3-4.5 points): a patient determined to be in the Intermediate Prognostic Risk Category is only allowable in the setting of ≥5% bone marrow myeloblasts.
- ECOG PS of 0, 1, or 2.
- Patients with AML (20%-30% blasts) must have a treatment-related mortality (TRM) score ≥4 for intensive, induction chemotherapy as calculated using the simplified model described by Walter and coworkers [7]; see Appendix A.

  Calculation of TRM score:
  - 0 for (age <61 years), +2 for (age 61-70 years), +4 for (age >71 years).
  - + 0 for (PS=0), +2 for (PS=1), +4 for (PS >1).
  - + 0 for (platelets <50,000/µL), +1 for (platelets >50,000/µL).
- Clinical laboratory values within the following parameters (repeat within 3 days before the first dose of study drug if laboratory values used for randomization were obtained more than 3 days before the first dose of study drug):
  - Albumin >2.7 g/dL.
  - Total bilirubin ≤upper limit of the normal range (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5×ULN of the direct bilirubin.
  - Alanine aminotransferase and aspartate aminotransferase <2.5×ULN.
  - Creatinine clearance >50 mL/min.
  - Hemoglobin >8 g/dL. Patients may be transfused to achieve this value. Elevated indirect bilirubin due to posttransfusion hemolysis is allowed.

Main Criteria for Exclusion:

- Previous treatment for HR MDS or CMML, or low-blast AML with chemotherapy or other antineoplastic agents including hypomethylating agents such as decitabine or azacitidine. Previous treatment is permitted with hydroxyurea and with lenalidomide, except that lenalidomide may not be given within 8 weeks before the first dose of study drug.
- Acute promyelocytic leukemia as diagnosed by morphologic examination of bone marrow, by fluorescent in situ hybridization or cytogenetics of peripheral blood or bone marrow, or by other accepted analysis.
- Patients with AML with a white blood cell count >50,000/ µL. Patients who are cytoreduced with leukapheresis or with hydroxyurea may be enrolled if they meet the eligibility criteria.
- Eligible for intensive chemotherapy and/or allogeneic stem cell transplantation. The reason a patient is not eligible for intensive chemotherapy and/or allogeneic stem cell transplantation may consist of one or more of the following factors:
  - Age >75.
  - Comorbidities.
  - Inability to tolerate intensive chemotherapy (eg, patients with AML with 20%-30% blasts and TRM ≥4).
  - Physician decision (eg, lack of available stem cell donor).
- Patients with either clinical evidence of or history of central nervous system involvement by AML.
- Treatment with any investigational products or participation in any interventional studies within 14 days before the first dose of any study drug.
- Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone resection.

- Prothrombin time or activated partial thromboplastin time >1.5×ULN or active uncontrolled coagulopathy or bleeding disorder. Patients therapeutically anticoagulated with warfarin, direct thrombin inhibitors, direct factor Xa inhibitors, or heparin are excluded from enrollment.
- Treatment with strong cytochrome P450 3A inducers within 14 days before the first dose of pevonedistat.

Main Criteria for Evaluation and Analyses:

Primary Endpoint:

- EFS: time from randomization to the date of an EFS event (defined as death or transformation to AML in patients with MDS or CMML, whichever occurs first, and defined as death in patients with low-blast AML).

Key Secondary Endpoint:

- OS.

Other Secondary Endpoints:

- Six-month and 1-year survival rates.
- Thirty-day and 60-day survival rates.
- Time to AML transformation in patients with HR MDS, patients with HR CMML, and patients with HR MDS/CMML.
- Rate of CR (CR in patients with HR MDS or CMML, or low-blast AML), CR+CRi in patients with low-blast AML, CR+marrow CR (in patients with HR MDS or CMML), CR+PR+HI (in patients with HR MDS or CMML), CR+marrow CR+PR (in patients with HR MDS or CMML), CR+marrow CR+PR+HI (in patients with HR MDS or CMML), overall response, overall response by Cycle 6, and overall response 2. Overall response in patients with HR MDS or CMML is defined as CR+PR; overall response in patients with low-blast AML is defined as CR+CRi+PR. Overall response 2 in patients with HR MDS or CMML is defined as CR+PR+HI; overall response 2 in patients with low-blast AML is defined as CR+CRi+PR.
- Duration of CR (CR for HR MDS or CMML, or low-blast AML), CR+CRi for low-blast AML, overall response (CR+PR for HR MDS or CMML, CR+CRi+PR for low-blast AML), and overall response 2 (CR+PR+HI for HR MDS or CMML, CR+CRi+PR for low-blast AML).
- Rates of RBC and platelet transfusion independence.
- Duration of RBC transfusion independence, platelet transfusion independence, and platelet and RBC transfusion independence.
- Time to first CR or PR or CRi (for patients with low-blast AML)
- Rates of HI in patients with HR MDS, patients with HR MDS/CMML, and patients with HR CMML.
- Patients who have inpatient hospital admission(s) related to HR MDS, CMML (collected through transformation to AML or until initiation of subsequent therapy, whichever occurs first) or low-blast AML (collected through initiation of subsequent therapy).
- Time to PD, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death.
- HRQOL assessed using the EORTC QLQ-C30.
- Plasma concentration-time data for pevonedistat.
- ORR, EFS, and OS in patients who have *TP53* mutations, 17p deletions, and/or are determined to be in an adverse cytogenetic risk group in both treatment arms.

There is 1 primary endpoint of EFS and 1 key secondary endpoint of OS. The study design employs an adaptive event-size re-assessment approach for EFS in patients with HR MDS and a multiple hierarchical testing procedure for type I error control.

There are 2 planned interim analyses (IAs) and 1 final analysis (FA). The first interim analysis (IA1) is to evaluate EFS for futility and perform EFS event size re-assessment for patients with HR MDS for the second interim analysis (IA2). IA2 will be an EFS FA in patients with HR MDS (US submission) and the intent-to treat (ITT) population (ex-US submission). The FA will evaluate OS.

IA1 will be performed when approximately 74 EFS events have occurred in patients with HR MDS (around 50% information relative to the minimal planned event size of 147 EFS events for patients with HR MDS for the EFS FA at IA2). The study will stop if the EFS hazard ratio is >1.0 in all 3 of the following populations: patients with HR

MDS, patients with HR MDS/CMML, and the ITT population. Otherwise, EFS event size re-estimation for patients with HR MDS will be performed using conditional power for the EFS FA that will be conducted at IA2.

IA2 (ie, EFS FA) will be performed when the approximate adaptive EFS event size (from a minimum of 147 to a maximum of 249), informed by the Independent Data Monitoring Committee, has occurred in patients with HR MDS. The FA will be performed when approximately 202 OS events have occurred in patients with HR MDS. Separate multiple hierarchical testing procedures for the US submission and the ex-US submission will be adopted to test the primary endpoint of EFS and the key secondary endpoint of OS in the HR MDS population (US submission), the ITT population (ex-US submission), and other disease populations at IA2 and FA, with each procedure having a total 1-sided alpha of 0.025. The details are described in Section 13.1.3.3.

Cui-Hung-Wang (CHW) [8] weighted log-rank test statistics will be used for all the tests that compare the treatment groups to preserve type-I error rate when the EFS event size in patients with HR MDS is re-estimated for IA2 at IA1. EFS in the HR MDS population (US submission) and in the ITT population (ex-US submission) will be tested first, only at IA2, using the 1-sided alpha of 0.025. All other tests specified in the multiple hierarchical testing procedures that will be performed at IA2 and/or FA, including OS in the HR MDS population (US submission), OS in the ITT population (ex-US submission), OS in the low-blast AML population, and OS in the HR MDS/CMML population, will use a 1-sided alpha of 0.0001 at IA2 and the remaining 1-sided alpha of 0.0249 at FA. The multiple testing procedure (multiple hypotheses and multiple looks) maintains control of the familywise type I error rate, as discussed in Glimm et al [9].

If the prespecified number of approximately 202 OS events for FA are expected (based on blinded study data) to be available close to the IA2, the IA2 (ie, EFS FA) and the FA (ie, OS FA) will be performed as a single analysis, when approximately 202 OS events and the adaptive EFS event size have occurred in patients with HR MDS. As originally planned, separate multiple hierarchical testing procedures for the US submission and the ex-US submission will be used to test the primary endpoint of EFS and the key secondary endpoint of OS in the HR MDS population (US submission), the ITT population (ex-US submission), and other disease populations at this single analysis, with a total 1-sided alpha of 0.025 for each procedure.

Sample Size Justification: The total number of patients was calculated on the basis of maintaining 83% power to test the key secondary endpoint OS in patients with HR MDS at a 1-sided alpha level of 0.025, as well as sufficient representation of patients with low-blast AML. The study is also adequately powered to test the primary endpoint, EFS in both patients with HR MDS and the ITT population for full approval in the US submission and the ex-US submission respectively, as well as to test OS in the ITT population.

A total of approximately 450 patients, including at least 350 patients with HR MDS or CMML and at least 100 patients with low-blast AML, will be enrolled. Patients will be randomized in a 1:1 ratio to the 2 treatment arms, stratified by low-blast AML, IPSS-R risk group of very high, high, or intermediate for MDS/CMML [1]. Assuming an enrollment rate that increases from an initial 1 patient per month to 22 patients per month after the first 10 months, with a dropout rate of approximately 10%, the study will take approximately 27 months for patient accrual and an additional approximately 38 months for follow-up from the enrollment of the last patient.

Assuming an exponential distribution for EFS, an initial minimum of 147 EFS events from patients with HR MDS will be required to detect an optimistic hazard ratio of 0.585 (median EFS of 17.09 months in the combination arm versus 10 months in the azacitidine alone arm) with approximately 90% power at a 1-sided alpha of 0.025. A maximum of 249 EFS events from patients with HR MDS will be needed to detect a hazard ratio of 0.663 (median EFS of 15.08 months in the combination arm versus 10 months in the azacitidine alone arm), with approximately 90% power at a 1-sided alpha of 0.025. The number of EFS events from patients with HR MDS for the adaptive EFS FA falls between the minimum of 147 EFS events and the maximum of 249 EFS events. It is projected that the EFS event size from the ITT population ranges from approximately 158 (approximately 92% power, 1-sided alpha=0.025, hazard ratio=0.585, median EFS of 22.22 months in the combination arm versus 13 months in the azacitidine alone arm) to 305 (approximately 95% power, 1-sided alpha=0.025, hazard ratio=0.663, median EFS of 19.61 months in the combination arm versus 13 months in the azacitidine alone arm).

Similarly, assuming an exponential distribution for OS, 202 OS events in patients with HR MDS will be needed to detect a hazard ratio of 0.663 (median OS of 36.95 months in the combination arm versus 24.5 months in the azacitidine alone arm), with approximately 83% power at a 1-sided alpha of 0.025. It is projected that approximately

280 OS events will occur to the ITT population, providing approximately 93% power to test OS in the ITT population (1-sided alpha=0.025, hazard ratio=0.663, median OS of 36.95 months in the combination arm versus 24.5 months in the azacitidine alone arm).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Coordinating Investigator

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

3.3 List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_t	area under the plasma concentration-time curve from time 0 to time t.
BCRP	breast cancer resistance protein
BSA	body surface area
BUN	blood urea nitrogen
CCR	conventional care regimen
CDL	cullin-dependent ubiquitin E3 ligase
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CMML	chronic myelomonocytic leukemia
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CRO	contract research organization
CHW	Cui-Hung-Wang (test)
CYP	cytochrome P450
DDI	drug-drug interaction
DLTs	dose-limiting toxicities
DME	drug-metabolizing enzyme
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
EQ-5D-5L	EuroQoL 5 dimensions 5 levels (a quality of life questionnaire of the "EuroQoL Group Association" that was expanded to a 5-level instrument)
EORTC	European Organisation for the Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Core Quality of Life Questionnaire
EOT	end of treatment
EU	European Union
ex-US	all countries and regions excluding the United States
FA	final analysis
FAB	French-American-British

Abbreviation	Term
FDA	[United States] Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
HI	hematologic improvement
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HR MDS	higher-risk myelodysplastic syndromes
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
IA	interim analysis
IA1	first interim analysis
IA2	second interim analysis
IB	Investigator's Brochure
IC_{50}	concentrations producing 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRC	independent review committee
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
ITT	intent-to-treat
ITD	internal tandem duplication
IV	intravenous(ly)
IWG	International Working Group
IWRS	interactive web response system
K-M	Kaplan-Meier
LFT	liver function test
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEDD8	neural precursor cell expressed developmentally down-regulated protein 8
NGS	next-generation sequencing
OATP	organic anion-transporting polypeptides
OBF	O'Brien Fleming

Abbreviation	Term
ORR	overall response rate
ORR 2	overall response rate 2
OS	overall survival
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	progressive disease; disease progression
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PP	per protocol
PR	partial remission
PRO	patient-reported outcome
PS	[Eastern Cooperative Oncology Group] performance status
PT	prothrombin time
PTA	posttrial access
PTE	pretreatment event
RAEB	refractory anemia with excess blasts
RAEB-t	refractory anemia with excess blasts in transformation
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDV	source data verification
SmPC	Summary of Product Characteristics
SOC	system organ class
SOE	Schedule of Events
SUSARs	suspected unexpected adverse reactions
TDC	Takeda Development Center
TEAE	treatment-emergent adverse event
TRM	treatment-related mortality
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Americas	Takeda Development Center Americas, Inc.
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC	TDC Americas, TDC Japan, TDC Asia, and/or TDC Europe, as applicable

4.0 INTRODUCTION

4.1 Scientific Background

4.1.1 Diseases Under Treatment

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

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

MDS are classified using the World Health Organization (WHO) classification system [6,10] based upon a combination of morphology, immunophenotype, genetics, and clinical features. The WHO classification system was built upon the French-American-British (FAB) Cooperative Group classification [5].

MDS are commonly divided into lower- or higher-risk categories based on the Revised International Prognostic Scoring System (IPSS-R) for MDS, which is a scoring system useful for estimating overall survival (OS) and the risk of transformation to AML [1]. Overall, approximately 25% of patients with very high, high, or intermediate IPSS-R scores will transform to AML within 0.7 years, 1.4 years, and 3.2 years, respectively [1]. Median survival for patients with MDS varies from years to months and decreases with increasing IPSS-R score.

Because MDS are heterogeneous diseases, varied treatment options exist. Most patients with MDS are managed with noncurative treatment strategies to control symptoms, improve quality of life, improve OS, and decrease progression to AML. Treatment of patients with lower-risk MDS (often defined as patients with <5% myeloblasts and/or normal or good risk cytogenetics and few cytopenias) focuses on minimizing blood product transfusions and maximizing quality of life through use of supportive care (eg, antibiotics as needed for infections, red blood cell [RBC] transfusions), growth factors such as erythropoiesis stimulating factors or immunosuppressive drugs. Treatment for patients with higher-risk disease often includes DNA hypomethylating agents (HMAs; azacitidine and decitabine) [11]. Rarely, intensive chemotherapy is used in patients with higher-risk MDS (HR MDS), but it generally results in significant toxicity and

modest responses (uptodate.com/contents/treatment-of-high-or-very-high-risk-myelodysplastic-syndromes, Treatment of high or very high risk myelodysplastic syndromes, Accessed 08 December 2014) [12-14].

Hypomethylating agents produce objective hematologic responses in approximately half of MDS patients, delay leukemic progression, improve quality of life, and, for azacitidine only, prolong survival in patients with HR MDS. Nevertheless, treatment with HMAs is not curative, and most patients relapse within 2 years. Lenalidomide, an immunomodulatory thalidomide congener, significantly improves RBC transfusion-independence rates and increases hemoglobin, but it is approved only for use in patients with the 5q syndrome subtype of low-risk MDS [12,13,15-17].

The only known curative therapy for MDS is allogeneic stem cell transplantation. However, only a minority of patients (typically with HR MDS) undergo this procedure because of contraindications and the limited availability of appropriate stem cell donors [18]. Even in these patients, treatment-related mortality (TRM) and morbidity and high relapse rates compromise long-term disease-free survival (uptodate.com/contents/treatment-of-high-or-very-high-risk-myelodysplastic-syndromes, Treatment of high or very high risk myelodysplastic syndromes, Accessed 08 December 2014) [13,19,20]. More-recent therapeutic approaches to MDS patients with higher-risk disease have involved combining drugs with HMAs, either to take advantage of synergistic properties of, for example, histone deacetylase inhibition combined with epigenetic modification, or to capitalize on nonoverlapping mechanisms of action [21,22].

As detailed by Zandberg et al, 2013 [23], chronic myelomonocytic leukemia (CMML) is a clonal stem cell disorder that displays features of both MDS and a myeloproliferative neoplasm. Diagnostic criteria for CMML include persistent peripheral blood monocytosis ($>10\times10^9$/L), absence of the Philadelphia chromosome and/or BCR-ABL1 fusion gene, absence of platelet-derived growth factor receptor or gene rearrangement, fewer than 20% blasts in the blood and the bone marrow, and dysplasia of 1 or more myeloid lineages [24]. CMML was classified as an MDS in the FAB classification system in 1982 [5], but was subsequently reclassified as a mixed myelodysplastic/myeloproliferative disorder by the WHO classification system in 2001 [25]. Two subgroups of CMML were proposed based on the white blood cell (WBC), a myelodysplastic type (WBC less than 13×10^9/L), and a myeloproliferative type (WBC greater than 13×10^9/L) [26]. CMML shares clinical and biological features with MDS, including development of cytopenias and bone marrow failure, risk of progression to AML, and overlapping recurring cytogenetic abnormalities. Like MDS, it has a variable clinical course, with reported rates of transformation to AML of 15% to 52% and a median OS of 12 to 18 months [27-29]. Treatment modalities for the 2 diseases are also similar, including hematopoietic growth factors (erythropoiesis-stimulating agents and granulocyte colony-stimulating factor [G-CSF]), transfusion support, HMAs, and allogeneic hematopoietic stem cell transplantation (HSCT).

Prognostic scoring systems for MDS, including the IPSS-R scoring system used in this study, have been routinely applied to patients with CMML and have been shown to be predictive of both transformation to AML and OS [30].

Low marrow blast count (20%-30%) WHO-defined AML was previously classified as refractory anemia with excess blasts (RAEB) in transformation (RAEB-t). WHO criteria now define AML as >20% bone marrow blasts. In a phase 3 randomized trial, azacitidine significantly prolonged OS compared with conventional care regimens (CCRs) in patients with HR MDS [16]. A subgroup analysis of 113 elderly patients (median age 70 years) compared the effects of azacitidine versus CCRs on OS of these FAB-defined RAEB-t and WHO-defined AML [16]. Median OS for azacitidine-treated patients was 24.5 months compared with 16.0 months for CCR-treated patients (hazard ratio=0.47). Furthermore, azacitidine was associated with fewer total days in the hospital than CCR. In another phase 3 study, 191 patients with HR MDS by FAB criteria were randomly assigned to azacitidine or best supportive care [31]. Of these, 45 patients had WHO-defined AML. Response rates to azacitidine were similar in MDS and these low marrow blast AML patients. Azacitidine was associated with improvements in physical function, symptoms, and psychological state. Patients assigned to supportive care were permitted to cross over to azacitidine at the time of progression; this design limited survival analysis. Based on these studies, azacitidine-based therapy is a standard of care in low marrow blast count WHO-defined AML.

While HR MDS, CMML, and low marrow blast count AML can have differences in clinical presentation and disease course, the biology of this group of diseases share similarities including mutations in genes such as *TP53*, *RUNX1*, *ASXL1*, and *TET2* [32-34]. This group of diseases, in addition to biological similarities, also shares, as previously discussed, sensitivity to azacitidine which results in clinical efficacy as demonstrated by significant improvements in overall response rates (ORRs), hematopoietic improvement and a significant improvement in OS compared with CCRs and with supportive care. The latter data, as well as preliminary clinical activity demonstrated by the combination of pevonedistat and azacitidine in previously untreated patients with AML (see Section 4.3), provide a compelling rationale to evaluate this combination in patients with HR MDS or CMML, or low marrow blast count AML.

4.1.2 Study Drug: Pevonedistat

Pevonedistat (MLN4924; TAK-924) is a first-in-class small molecule inhibitor of the neural precursor cell expressed developmentally down-regulated protein 8 (NEDD8)-activating enzyme that is being developed for the treatment of malignancies. NEDD8-activating enzyme (NAE) is an E1 activating enzyme and is an essential component of the NEDD8 conjugation pathway, which controls the activity of a subset of ubiquitin E3 ligases, multiprotein complexes that transfer ubiquitin molecules to protein substrates that are then targeted to the proteasome for degradation. Cullin-dependent ubiquitin E3 ligases (CDLs) require conjugation to NEDD8 to be activated. CDLs control the timely ubiquitination and consequent proteasomal degradation of proteins with important roles in cell cycle progression and signal transduction, cellular processes that are integral to tumor cell growth, proliferation, and survival. Inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers by disrupting proteasomal degradation of a variety of critical regulatory proteins. As detailed in Section 4.5, the nonclinical and preliminary clinical experience in AML with pevonedistat alone or in combination supports further evaluation in the subset of patients who are classified as HR MDS or CMML, or low-blast AML.

4.2 Nonclinical Experience

4.2.1 Single-Agent Pevonedistat

Pevonedistat is a potent and selective inhibitor of NAE activity.

Pevonedistat treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines derived from acute leukemias, lymphomas, multiple myeloma, and a range of solid tumor types. Changes in protein levels observed in cultured cells treated with pevonedistat were consistent with the inhibition of NAE, in particular a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CDL substrates, including NFE2-related factor 2 and chromatin-licensing and DNA-replication factor-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 [35-37].

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

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

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

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

4.2.2 Pevonedistat With Azacitidine

The combination of pevonedistat with azacitidine demonstrated synergistic or additive effects on viability of AML cell lines treated in vitro. Combination index analysis demonstrated synergy of pevonedistat with azacitidine in 2 AML cell lines (OCI-M2 and NB-4) and additivity in 2 additional AML cell lines (THP-1 and HL60). The combination of pevonedistat and azacitidine in HL60 and OCI-M2 cell lines resulted in increased DNA damage (measured by phospho-H2AX) and apoptosis (measured by cleaved caspase-3) compared with the levels of these markers induced by single-agent pevonedistat or azacitidine.

The benefit of the combination of pevonedistat with azacitidine was confirmed in vivo with immunocompromised mice bearing HL-60, OCI-M2, and THP-1 SC tumor xenografts. Pevonedistat in combination with azacitidine demonstrated additive or synergistic antitumor activity and tumor regression in all 3 SC xenograft models, which represent both azacitidine-sensitive (OCI-M2) and azacitidine-insensitive (HL60 and THP-1) models. In OCI-M2, azacitidine and pevonedistat as single agents inhibited tumor growth, but the combination of these agents resulted in tumor regressions with a statistical assessment of synergy. In THP-1, although pevonedistat as a single agent inhibited tumor growth without causing regressions and azacitidine as a single agent had only a marginal effect on tumor growth, the combination caused regressions and delayed tumor regrowth following the treatment period. In HL60, tumor regressions were seen with the combination of pevonedistat and azacitidine at dose levels that had minimal or moderate antitumor activity as single agents. Furthermore, in a disseminated xenograft model in which HL60 cells were inoculated into immunocompromised mice by IV injection, pevonedistat and azacitidine as single agents both extended survival time compared with a control group, but the combination extended survival time longer than would be expected from an additive combination, thereby demonstrating a synergistic effect on survival.

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

4.3 Clinical Experience

As of 22 January 2018, pevonedistat has been administered to approximately 495 patients in clinical studies. These include 227 patients diagnosed with advanced malignancies including solid tumors, AML, melanoma, lymphoma, multiple myeloma, HR MDS, and acute lymphoblastic leukemia who participated in studies of single-agent pevonedistat. In completed combination studies, 64 elderly patients with treatment-naïve AML (Study C15009) were treated with pevonedistat plus azacitidine, and 64 patients with solid tumors received combination treatments with docetaxel, gemcitabine, or a combination of carboplatin and paclitaxel (Study C15010). In ongoing combination studies, 51 patients with advanced solid tumors have received a single IV dose of pevonedistat alone and in combination with the cytochrome P450 (CYP) 3A inhibitor probes itraconazole or fluconazole (36 of these 51 patients then continued receiving pevonedistat plus standard of care, either docetaxel, or carboplatin plus paclitaxel) (Study C15011); 23 East Asian patients with WHO-defined AML or HR MDS have received a single IV dose of pevonedistat alone and in combination with azacitidine (Study Pevonedistat-1012); 6 patients with

advanced solid tumors have received a single dose of [^{14}C]-pevonedistat (5 of these 6 patients then continued receiving pevonedistat plus standard of care, either docetaxel, or carboplatin plus paclitaxel) (Study Pevonedistat-1013); and 58 patients with HR MDS, CMML, or low-blast AML have received combination treatment with azacitidine and pevonedistat (Study Pevonedistat-2001).

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

Pevonedistat has clinical activity when administered in combination with azacitidine. Study C15009 evaluated the combination of escalating doses of pevonedistat plus azacitidine in 64 treatment-naïve patients with AML. The maximum tolerated dose (MTD) was determined to be 20 mg/m^2 pevonedistat in combination with 75 mg/m^2 azacitidine. A total of 61 patients were treated at the MTD. ORR in the 64-patient intent-to-treat (ITT) cohort was 50% (20 CR, 5 complete remission with incomplete blood count recovery [CRi], 7 PR) with an 8.3 month median duration of remission. Pevonedistat PK was not altered by the addition of azacitidine. The nature and frequency of the reported toxicities (excluding DLTs) were similar to previous reports for azacitidine alone. [38].

Additional efficacy and safety information from Study C15009 is provided in Section 4.6.2.

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

4.4 PK of Pevonedistat

4.4.1 Nonclinical PK and Risk Assessment for Drug-Drug Interactions

The absorption, distribution, metabolism, and excretion properties of pevonedistat have been studied in Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and chimpanzees. The whole blood clearance is low in all animal species, likely as a result of the extensive partitioning of pevonedistat into RBCs. The plasma terminal disposition half-life varied from short (less than 1 hour in rats) to relatively long (15 hours in monkeys). The major elimination pathway of

pevonedistat in animals is through the hepatic route. Urinary excretion of unchanged pevonedistat was negligible (<5%) in rats and primates. After an IV dose of [^{14}C] pevonedistat, radioactivity was primarily excreted in the feces in intact rats and in bile duct-cannulated rats; excretion was almost complete by 24 hours postdose. No plasma metabolite accounted for more than 10% of the total plasma radioactivity, suggesting potentially low systemic exposure to metabolites.

In vitro, pevonedistat is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters and is metabolized via hydroxylation and oxidation, predominantly by CYP3A4, with a small contribution from CYP2D6 (approximately 3%). Study C15011 is an open-label, 2-arm, phase 1 study to assess the effects of multiple doses of fluconazole, a moderate CYP3A inhibitor, and itraconazole, a strong CYP3A/P-gp inhibitor, on the single-dose PK of pevonedistat in patients with advanced solid tumors. 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 that 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. Strong and moderate CYP3A inhibitors and P-gp inhibitors can be used in patients receiving pevonedistat.

On the basis of completed in vitro studies, pevonedistat is predominantly metabolized through CYP3A-mediated pathways, as evidenced by the findings in human hepatic S9 fractions and recombinant CYP isozyme incubations. The contribution of CYP3A to pevonedistat clearance is minor on the basis of preliminary results of Study C15011. The effect of rifampin, a strong CYP3A inducer, on pevonedistat PK was evaluated in Study Pevonedistat-1015 (P1015). Co-administration of rifampin did not result in clinically meaningful alteration of pevonedistat systemic exposures. Based on findings from Study P1015, as of Amendment 07, administration of pevonedistat with strong CYP3A inducers is permitted in the ongoing and planned clinical studies.

In vitro, pevonedistat is a substrate for the drug efflux transporters P-gp and BCRP and is also a weak inhibitor of BCRP-mediated transport (concentrations producing 50% inhibition [IC_{50}] of 6.3 μM). Additional transport studies with organic anion-transporting polypeptides (OATP) in sandwich-cultured human hepatocytes showed that pevonedistat can inhibit the hepatic uptake of estrone-3-sulfate (IC_{50} of 29.1 μM) while inhibition of OATP-mediated uptake of simvastatin and lovastatin (IC_{50} of 0.4-4.9 μM and 0.9 μM, respectively) was observed in some, but not all, donors. On the basis of these data, pevonedistat at clinically relevant concentrations is unlikely to affect the PK of other drugs that are known BCRP or OATP substrates (IC_{50} >10-fold the unbound C_{max} even with the lowest estimated value). In addition, the effect of BCRP inhibition is not expected to be clinically meaningful. Refer to Section 4.6.3 for a summary of potential clinical drug-drug

interactions (DDIs), and Sections 8.4 and 8.5 for excluded and permitted concomitant medications in this study.

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

4.4.2 Clinical PK

Clinical PK data are summarized in Section 5.2 of the IB. Single- and multiple-dose PK of pevonedistat have been evaluated in adult patients with solid tumors or hematologic malignancies. In these studies, pevonedistat was administered IV at dose levels of 25 to 278 mg/m^2 and with various daily or intermittent dosing schedules within 21-day treatment cycles. Plasma concentrations of pevonedistat declined in a multi-exponential manner at the end of a 1-hour IV infusion, with little or no notable drug accumulation upon repeat dosing. This observation is consistent with a mean terminal elimination half-life of approximately 10 hours (range, 7.7-15.2 hours) estimated across doses and schedules. Pevonedistat PK was linear over the dose range studied based on an area under the plasma concentration-time curve (AUC) from time 0 to 24 hours that increased proportionately with dose. Consistent with in vitro data, pevonedistat was also found to extensively partition in human blood (mean blood-to-plasma concentration ratio of ~65) with observed concentrations of pevonedistat in whole blood and plasma declining in parallel over 24 hours. Upon exploration of the effects of patient-specific covariates on pevonedistat population PK, body size and age influenced clearance of pevonedistat, while only body size was important for all volume of distribution parameters. Additionally, data are available in 29 treatment-naïve, elderly AML patients who received IV pevonedistat at 20 mg/m^2 (n=26) and 30 mg/m^2 (n=3) on Days 1, 3, and 5 in combination with IV/SC azacitidine 75 mg/m^2 on a 5-on/2-off (weekend)/2-on schedule (Study C15009) [39]. These data indicate that pevonedistat PK remains unaffected by 5 continuous days of azacitidine dosing when compared with single-agent pevonedistat data from the earlier study in AML patients (Study C15003).

4.5 Rationale for the Proposed Study

MDS include a heterogeneous group of myeloid disorders characterized by ineffective hematopoiesis and transformation to AML. Treatment with azacitidine increases OS in patients with HR MDS relative to conventional care [16]. Consequently, azacitidine is approved in many countries as a single agent in HR MDS.

Pevonedistat is an investigational, first-in-class inhibitor of the NAE that has reported single-agent clinical activity in a phase 1 study in relapsed/refractory AML patients [40]. Based on nonclinical studies in AML models that demonstrated a synergistic lethality in cell lines and tumor regression in murine xenografts when pevonedistat was combined with azacitidine, pevonedistat has been studied in combination with azacitidine in treatment-naïve elderly AML patients who are unlikely to benefit from standard induction therapy (Study C15009). Results demonstrate that 20 mg/m^2 pevonedistat plus azacitidine is generally well tolerated and demonstrates signs of clinical activity [39,41].

4.5.1 Rationale for Study Population

Given the overlapping treatments and pathophysiology between HR MDS and AML, this phase 3 study will evaluate event-free survival (EFS) (in HR MDS or CMML, an event is defined as transformation to AML or death; in-low-blast AML, an event is defined as death) of the combination of pevonedistat and azacitidine compared with single-agent azacitidine as a treatment for HR MDS or CMML, or low-blast AML. Patients with CMML are included because CMML shares clinical and biological features with MDS, has a similar variable clinical course, and treatment modalities for the 2 diseases are also similar (see Section 4.1.1). Patients with CMML were also included in randomized studies of azacitidine conducted in the United States (US) and the European Union (EU) with similar response rates to MDS patients [16,31]. The rationale for including low marrow blast count (20%-30%) WHO-defined AML is based on the fact that it had been previously classified as RAEB-t, which was part of the MDS spectrum, and that it is often treated with azacitidine-based therapy (see Section 4.1.1).

4.5.2 Rationale for the Combination of Pevonedistat Plus Azacitidine

The rationale for combining pevonedistat with azacitidine in patients with AML and MDS is 2-fold; namely, the single-agent activity observed with azacitidine [16] and pevonedistat [42] in patients with AML or related diseases such as MDS, and the preclinical evidence supporting the improved benefit of pevonedistat administered in combination with azacitidine in AML xenograft models; see Section 4.2.2 and the IB for more information.

4.5.3 Rationale for Dose and Schedule of Study Drugs

The choice of doses and schedules for this study was based on Study C15009, which established the MTD of pevonedistat as 20 mg/m^2 given on Days 1, 3, and 5, in combination with 75 mg/m^2 azacitidine given on Days 1 through 5, 8, and 9, in 28-day treatment cycles. The DLTs supporting this determination were elevations in liver function tests (LFTs); see Section 4.3 and the IB for more information.

The commonly used schedule of azacitidine administration in the US is a 5-on/2-off (weekend)/2-on schedule to avoid the logistical limitations associated with administering drugs to patients during the weekend. According to oncologist/hematologist surveys conducted by the sponsor, of the patients treated with azacitidine for AML in the US, approximately 70% follow this schedule. Garcia-Delgado et al conducted a retrospective evaluation of 3 schedules of azacitidine administration to 240 patients with WHO-defined MDS or AML with 20%-30% bone marrow blasts. Patients were treated with azacitidine, on 1 of the following 3 dosage regimens: 5 consecutive days (AZA 5); 7 days including a 2-day break (AZA 5-2-2); or 7 consecutive days (AZA 7)—all 28-day cycles. ORRs for the AZA 5, AZA 5-2-2, and AZA 7 schedules were 39.4%, 67.9%, and 51.3%, respectively, and median OS durations were 13.2, 19.1, and 14.9 months, respectively. These results suggest better effectiveness and tolerability profiles for 7-day schedules and at least comparable and possibly superior efficacy of the AZA 5-2-2 schedule compared with the AZA 7 schedule [43].

In this study, azacitidine may be administered using either the SC or IV route of administration, given that comparable systemic exposures (AUC_{48}) to pevonedistat were achieved following either route by which azacitidine was given in Study C15009. Furthermore, it has been shown that azacitidine exposures and efficacy are comparable regardless of the route of azacitidine administration [44-46].

As detailed in Section 4.3, some patients in Study C15003 (single-agent pevonedistat in patients with relapsed/refractory AML) derived clinical benefit from continuing study treatment despite increases in their bone marrow blast counts while on treatment. Standard MDS guidelines [47] also recommend treatment for 6 cycles without altering dose or frequency of azacitidine regardless of cytopenias. Patients with HR MDS or CMML may be allowed to continue study treatment (either treatment arm) if they meet the criteria for progressive disease (PD) based only on bone marrow blast count (without AML transformation) if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients with low-blast AML in this study may also be allowed to continue study treatment (either treatment arm), even if they meet the criteria for PD based only on bone marrow blast counts, if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment. If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study.

4.5.4 Rationale for Molecular Analyses

Analysis of Biomarkers in Bone Marrow Aspirate

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

The European LeukemiaNet integrates cytogenetics and molecular features of 3 key AML genes (FLT3 internal tandem duplication [ITD], CEBP, and NPM1) to classify patients into 3 prognostic risk groups [48]. As more genomic data from AML patients—from those who are newly diagnosed as well as those who have relapsed after standard of care therapy—become available, additional mutations in genes such as ASXL1 and TET2 are also being shown to have prognostic value [49,50]. Several novel risk-categorization schema have been proposed that include mutational status of these and other genes [51]. The IPSS-R for MDS now incorporates cytogenetics into the scoring system as a way to determine the risk of transformation to AML [1]. Additionally, there are several recurrent somatic mutations which are drivers of MDS pathogenesis and can be associated with clinical phenotype (eg, RNA splicing factor mutations in ring-sideroblasts) [52,53]. The assessment of mutations in several genes with known prognostic

significance is now more routinely incorporated into clinical practice, though this list will likely expand with increased knowledge of the genomic landscape of these diseases.

Mutational data are increasingly being used as a complementary tool to influence the selection of the most appropriate therapy, such as the consideration of small molecule FLT3 inhibitors for AML patients with tumor samples that test positive for the FLT3 ITD oncogene. The FLT3 ITD mutation is observed in approximately 30% of all AML cases [54]. Additional targeted therapies designed against specific AML mutations are currently in development. These include targeted agents against mutations in IDH1 and 2 present in approximately 8.5% and 7.5% of AML patients respectively [55]. It is likely that acquired mutations could also predict response to specific interventions, such as treatment with HMAs [56]. For example, it has recently been shown that mutations in *TET2* are associated with sensitivity to azacitidine, whereas patients with the wild-type *TET2* gene have been shown to be resistant to azacitidine [56-59]. In MDS, *TP53* mutations are associated with complex karyotype, elevated bone marrow blast percentage, and severe thrombocytopenia. However, in multivariate analysis, the presence of this abnormality has also been shown to have independent prognostic significance [56,60]. In a study published by Bejar et al [56], *TP53* mutation status was the most significant predictor of mortality after HSCT. Additionally, *TP53* mutations have also been shown to be independently prognostic in MDS patients treated with HMAs such as azacitidine. While *TP53*-mutated MDS patients initially respond well to HMAs, their duration of response is significantly shorter than wild-type patients [60]. In AML patients as well, though *TP53* is associated with older age, genomic complexity, specific DNA copy number alterations, and a monosomal karyotype, in multivariable analysis, *TP53* alterations are the most important prognostic factor in complex karyotype-AML, outweighing all other variables [61]. Based on these reports, finding therapies for AML and MDS patients with *TP53* mutations that can improve duration of response and OS represents an unmet medical need.

Epigenetic changes have also been implicated in the pathogenesis of AML and MDS. For example, accumulation of abnormal methylation is a dynamic process in MDS, with increasing levels of methylation associated with progression to RAEB and AML [62]; hence, it is likely that aberrant methylation actively contributes to MDS progression [63]. In recent years, recurrent somatic mutations in genes encoding proteins involved in DNA methylation and demethylation and in covalent histone modifications have been reported in several myeloid malignancies [63]. Azacitidine is a DNA methyltransferase inhibitor and could potentially target epigenetic changes in AML and MDS. Evaluating epigenetic modifications in bone marrow cells at Baseline and at specified time points after treatment has the potential to identify changes in epigenetic status that might correlate with response to the combination of pevonedistat and azacitidine. Throughout this study, Baseline assessments are defined as those performed at the closest time before the start of study drug administration.

Leukemic cells that remain in the bone marrow following treatment are a major cause of disease relapse. Minimal residual disease (MRD) testing provides the sensitivity and specificity to identify the presence of these residual cells and determine the depth and duration of response achieved following therapy. Studies have shown that the sensitive detection of a leukemia-specific marker (eg, a mutation in the gene encoding nucleophosmin, *NPM1*) could improve prognostication by

identifying submicroscopic disease during remission [64]. Measurement of MRD is receiving recognition as a potential tool to assess the quality of response after chemotherapy and to plan postremission strategies. Though polymerase chain reaction (PCR) and multiparametric flow cytometry have become the most popular methods to investigate MRD in AML [65] and techniques such as next-generation sequencing (NGS) are also being explored in both AML and MDS [33,48,66].

In this study, the baseline molecular alterations to be evaluated from bone marrow aspirate samples collected at Screening or before the administration of study drug may include, but are not limited to, cytogenetic abnormalities, changes in gene expression, DNA mutations, and epigenetic alterations. Molecular techniques such as, but not limited to, targeted sequencing using NGS will be used for these analyses. Correlative analyses of bone marrow molecular characteristics will be done to identify biomarkers linked to response to and/or safety of the combination of pevonedistat and azacitidine.

Similar analyses will be conducted in bone marrow samples from patients who initially respond to therapy and subsequently relapse. These analyses will allow the evaluation of potential mechanisms of treatment-emergent resistance, such as somatic mutations in NAE subunits and key signaling pathways, or change in pathway activity, in tumors that initially respond to therapy and then exhibit PD.

Changes in epigenetic status in the tumor cells following treatment with the combination of pevonedistat and azacitidine may be assessed by comparing epigenetic modification in bone marrow aspirate samples obtained at Screening and after treatment.

MRD assessments may be conducted on bone marrow aspirates collected at predefined early (eg, following Cycle 2 and Cycle 4) and late time points (eg, following Cycle 6 and Cycle 9) during the study. MRD or depth-of-response analysis may be done using Flow, proteomic, or NGS-based methods.

Analysis of Biomarkers in Blood

Though researchers have routinely analyzed bone marrow aspirates for cytogenetic and molecular abnormalities in patients with HR MDS, CMML and AML, several new methodologies are also being developed to analyze these aberrations in cells isolated from blood [67,68]. Based on these current developments, blood samples will also be collected at predefined time points and may be used for analysis of baseline molecular alterations (including cytogenetic abnormalities), depth of response, epigenetic alterations and changes in immune profile following therapy.

Analysis of Biomarkers in Buccal Epithelial Cell Samples

In this study, buccal epithelial cell samples will be collected at Screening. The DNA from the buccal epithelial cell samples will be used for characterization of genotype variations in genes encoding drug-metabolizing enzymes (DMEs) or transporters that might be implicated in pevonedistat disposition. It may also be used in the interpretation of the tumor DNA sequencing data.

It should be noted that the overall study results will dictate the extent to which some of the biomarker analyses described above will be conducted.

4.5.5 Rationale for Health-Related Quality of Life Assessments

When caring for patients with advanced and life threatening diseases such as cancer, preserving their health-related quality of life (HRQOL) and reducing symptom burden are among the most important therapeutic goals. Furthermore, patient-reported outcomes (PROs), such as physical functioning and symptoms, are increasingly important in clinical research, including in oncology [69] and hematology [70]. However, there are limited data on PROs among patients with MDS, CMML, and AML. In previous randomized clinical trials among patients with MDS, patients on the azacitidine arm experienced improvement in HRQOL as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) PRO instrument [71]. It is expected that the clinical activity of the combination of pevonedistat with azacitidine will lead to an improvement in patients' HRQOL, as well as other symptoms and reduce the impact on HRQOL for patients with MDS, CMML, and AML.

To compare the impact of treatment between the 2 patient groups in this study, HRQOL will be assessed by 2 instruments: EORTC QLQ-C30 and EuroQoL 5 dimensions 5 levels (a quality of life questionnaire of the "EuroQoL Group Association" that was expanded to a 5-level instrument) (EQ-5D-5L). Data from these 2 instruments will facilitate assessment of important general, cancer-specific, and MDS-specific HRQOL domains and items, and ascertainment of how these may be correlated with certain clinical outcomes.

The EORTC QLQ-C30 [72], designed to assess HRQOL in a wide range of cancer patient populations, has been administered in multiple randomized clinical trials of patients with MDS [71,73]. The EORTC QLQ-C30 instrument has been recommended for use in oncology trials [74] and is widely utilized in clinical trials and in global registries. Furthermore, regulatory agencies and health technology assessment bodies are increasingly considering PROs, such as physical functioning and symptoms, in their deliberations. Supplemental items from the EORTC item bank can also be included to cover relevant concepts not measured by the core EORTC QLQ-C30 questionnaire.

The EQ-5D-5L [75] is a self-reported preference-based measure of health developed to describe and value health across a wide range of disease areas and to inform economic evaluations. It is widely accepted by health technology assessment agencies worldwide.

Refer to Section 9.4.12 for additional details on the components and administration of these questionnaires.

4.6 Potential Risks and Benefits

4.6.1 Azacitidine

In clinical studies, adverse reactions to azacitidine were qualitatively similar between the IV and SC routes of administration [44]. In clinical studies with SC administration of azacitidine, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and

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

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

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

Refer to the VIDAZA (azacitidine) US Prescribing Information (USPI) [44],or the EU Summary of Product Characteristics (SmPC) [76], as applicable, for the most recent information regarding the anticipated risks and benefits of azacitidine.

4.6.1.1 Anemia, Neutropenia, and Thrombocytopenia

Azacitidine causes anemia, neutropenia, and thrombocytopenia. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, before each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response (see Section 8.3.2.1).

4.6.1.2 Severe Pre-existing Hepatic Impairment

Caution is needed in patients with liver disease when administering azacitidine. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L [77]. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

4.6.1.3 Renal Abnormalities

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

4.6.2 Pevonedistat Plus Azacitidine

Study C15009 evaluated the combination of escalating doses of pevonedistat on Days 1, 3, and 5 plus 75 mg/m^2 azacitidine administered (IV or SC) on a 5-on/2-off (weekend)/2-on schedule in

28-day cycles in treatment-naïve patients with AML, aged ≥60 years, who are unlikely to benefit from standard induction therapy [38].

A total of 64 patients were treated (ITT population) at 2 dose levels (median age 75 years [range 61-89]; 53% male; 77% Eastern Cooperative Oncology Group [ECOG] performance status [PS] 0/1, 22% ECOG PS 2; 56% de novo AML, 44% secondary AML). Median marrow blasts were 38.5% (range 5-92), 50% of patients had intermediate-risk, 28% had adverse-risk, and 3% had favorable-risk cytogenetics.

Pevonedistat dosing started at 20 mg/m^2 (n=6) and increased to 30 mg/m^2 (n = 3) in the absence of DLTs. During dose escalation, at the 30 mg/m^2 dose level, 2 of the 3 patients experienced a DLT: 1 patient had persistent Grade 2 bilirubin elevation, and 1 patient had reversible Grade 4 aspartate aminotransferase (AST) elevation. Transaminase and bilirubin elevations were transient and clinically inconsequential in both patients (resolving to Grade 1 or baseline levels within 1 week after withdrawal from study). The MTD was determined to be 20 mg/m^2 pevonedistat in combination with 75 mg/m^2 azacitidine. An additional 55 patients were treated at the MTD, for a total of 61 patients treated at the MTD.

Patients in the ITT cohort (n = 64) received a median of 4 cycles (range 1-37), and 23/64 patients (36%) received ≥6 cycles of pevonedistat+azacitidine. The most common adverse events (AEs) were constipation (48%), nausea (42%), fatigue (42%), and anemia (39%). Fifty-three patients (82%) experienced ≥Grade 3 AEs; the most frequent (≥15%) were anemia, febrile neutropenia (each 30%), thrombocytopenia (23%), neutropenia (20%), and pneumonia (17%). AST/alanine aminotransferase (ALT) elevations ≥Grade 3 were reported in 6% of patients. Forty-four patients (69%) experienced serious adverse events (SAEs); the most frequent (≥10%) were febrile neutropenia (25%) and pneumonia (14%). In addition to the 2 patients who withdrew because of DLTs, 2 patients withdrew from the study because of therapy-related toxicity (febrile neutropenia). In the MTD expansion cohort (n = 55), 2 additional patients experienced DLTs (≥Grade3 transaminase elevation) and were successfully rechallenged with a reduced dose of pevonedistat. Both patients remained on study without further hepatic toxicity. There were 11 on-study deaths unrelated to study therapy. Pevonedistat pharmacokinetics (PK) was not altered by the addition of azacitidine.

ORR in the 64-patient ITT cohort was 50% (20 CR, 5 CRi, 7 PR), with a median duration of remission of 8.3 months (95% CI: 5.52, 12.06). Of the responding patients, 63% (20/32) responded within the first 2 cycles of treatment, 14 had responses lasting ≥4 cycles, 2 went on to have allogeneic stem cell transplant. In total, 3 patients proceeded to stem cell transplantation, as they met physiologic requirements and agreed to pursue the treatment. ORR was 52% (13/25; 7 CR, 3 CRi, 3 PR) versus 49% (19/39; 13 CR, 2 CRi, 4 PR) for patients with low (<30%) versus high (≥30%) marrow blasts; 53% (19/36; 12 CR, 3 CRi, 4 PR) versus 46% (13/28; 8 CR, 2 CRi, 3 PR) for patients with de novo AML versus secondary AML; 44% (14/32; 9 CR, 1 CRi, 4 PR) versus 44% (8/18; 5 CR, 2 CRi, 1 PR) for patients with intermediate- versus adverse-risk cytogenetics; and 83% (19/23; 14 CR, 2 CRi, 3 PR) versus 32% (13/41; 6 CR, 3 CRi, 4 PR) for patients who received ≥6 cycles versus <6 cycles of azacitidine, respectively. Responses were seen in patients with typically refractory disease. In total, 6 of 8 patients with a *TP53* mutation achieved CR/CRi/PR, and 4 of 6

remained on study for >10 cycles. Among the entire cohort of 61 patients treated at the MTD (median follow-up of 21.2 months), survival was 52% at 6 months and 45% at 1 year; median OS was 7 months and 11.2 months versus 5.6 months for patients with secondary AML versus de novo AML. The median OS was 11.2 months versus 5.2 months for patients with low (<30%) versus high (≥30%) marrow blasts and 16.1 months versus 5.3 months for patients aged 65 to 74 versus ≥75 years, respectively.

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

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

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

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

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

Potential risks that are derived from findings in animal studies in rats and dogs include myocardial degeneration and thrombosis, cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure, increased diastolic blood pressure, pulmonary hypertension, enteropathy (including dehydration and electrolyte loss) with secondary sepsis, effects on testes and ovaries that represent a reproductive hazard including sterility, increased developmental risk to fetus or embryo, decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, high) (this finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the

doses), prolongation of the activated partial thromboplastin time (aPTT), and local tissue injury when administered SC. Additional details may be found in the current IB.

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

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

4.6.3 Potential for DDIs

No formal clinical assessments of DDIs between azacitidine and other agents have been conducted. Please consult the VIDAZA USPI (Clinical Pharmacology [Section 12.3], Drug-Drug Interactions) for additional information [44].

Pevonedistat PK in combination with azacitidine was assessed in 64 evaluable treatment-naïve patients with AML in Study C15009. Pevonedistat systemic exposures were not altered in the presence of azacitidine when compared with historical single agent data (Study C15003). The potential risk of DDIs between pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data (see IB). Study C15011, a phase 1 DDI study, is currently ongoing. The study assesses the effect of multiple doses of fluconazole (a moderate CYP3A inhibitor) as well as the effect of multiple doses of itraconazole (a strong CYP3A inhibitor) on the PK, safety, and tolerability of a single dose of IV pevonedistat (see Section 4.4.1). Based on preliminary assessments, administration of pevonedistat with moderate and strong CYP3A inhibitors and P-gp inhibitors is permitted in this study. In Study P1015, co-administration of rifampin, a strong CYP3A inducer, with pevonedistat did not result in clinically meaningful alteration of pevonedistat systemic exposures. Therefore, the use of strong CYP3A inducers is now permitted in this study. As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored as the DDI potential between pevonedistat and other drugs has not been formally studied in humans. Patients should also be instructed to consult with the investigator before taking any new medications, including over-the-counter products and herbal supplements.

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

4.6.4 Summary of Risks and Benefits

Analyses of safety data from more than 130 patients treated with pevonedistat plus azacitidine at the dose and schedule to be used in this phase 3 study demonstrate that pevonedistat adds little toxicity to azacitidine alone and that toxicities are manageable. Efficacy data from a phase 1 study using this combination demonstrated a 50% ORR based on an ITT analysis (20 CR, 5 CRi, 7 PR), with an 8.3-month median duration of remission in untreated, older patients with AML for whom intensive induction chemotherapy was considered inappropriate. In patients receiving ≥6 cycles of

therapy (n = 23, 44%), ORR was 83%. In total, 6 out of 8 patients with a *TP53* mutation achieved CR/CRi/PR, and 4 of 6 remained on study for >10 cycles. Baseline bone marrow blast percentage or cytogenetic/molecular risk did not influence ORR [38]. Thus, the benefit-risk ratio supports further study of the combination of pevonedistat and azacitidine in a randomized controlled trial in patients with HR MDS or CMML, or AML.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objective is:

- To determine whether the combination of pevonedistat and azacitidine improves EFS when compared with single-agent azacitidine. (An event is defined as death or transformation to AML in patients with MDS or CMML, whichever occurs first, and is defined as death in patients with low-blast AML.)

5.1.2 Key Secondary Objective

The key secondary objective is:

- To determine whether the combination of pevonedistat and azacitidine improves OS when compared with single-agent azacitidine.

5.1.3 Other Secondary Objectives

Other secondary objectives are:

- To determine whether the combination of pevonedistat and azacitidine improves 6-month and 1-year survival rates when compared with single-agent azacitidine.
- To determine in patients with HR MDS, patients with HR CMML, and patients with HR MDS/CMML whether the combination of pevonedistat and azacitidine delays time to AML transformation when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves the rate of CR (CR in patients with HR MDS or CMML, or low-blast AML), CR+CRi in patients with low-blast AML, CR+marrow CR (in patients with HR MDS or CMML), CR+PR+hematologic improvement (HI) (in patients with HR MDS or CMML), CR+marrow CR+PR (in patients with HR MDS or CMML), CR+marrow CR+PR+HI (in patients with HR MDS or CMML), overall response, overall response by Cycle 6, and overall response 2. Overall response in patients with HR MDS or CMML is defined as CR+PR; overall response in patients with low-blast AML is defined as CR+CRi+PR. Overall response 2 in patients with HR MDS or CMML is defined as CR+PR+HI; overall response 2 in patients with low-blast AML is defined as CR+CRi+PR.

- To determine whether the combination of pevonedistat and azacitidine, when compared with single-agent azacitidine, improves duration of CR (CR for HR MDS or CMML, or low-blast AML), CR+CRi for low-blast AML, overall response (CR+PR for HR MDS or CMML, CR+CRi+PR for low-blast AML), and overall response 2 (CR+PR+HI for HR MDS or CMML, CR+CRi+PR for low-blast AML).
- To determine whether the combination of pevonedistat and azacitidine improves rate of transfusion independence when compared with single-agent azacitidine. RBC and platelet transfusion independence requires that the patient receive no RBC or platelet transfusions for a period of at least 8 weeks during the time period from the first dose of study drug administration through 30 days after the last dose of any study drug.
- To determine whether the combination of pevonedistat and azacitidine increases the duration of RBC transfusion independence, platelet transfusion independence, or platelet and RBC transfusion independence, when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine improves time to first CR or PR or CRi (in patients with low-blast AML) when compared with single-agent azacitidine.
- To determine in patients with HR MDS, patients with HR MDS/CMML, and patients with HR CMML whether the combination of pevonedistat and azacitidine improves rates of HI when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine does not increase inpatient hospital admission related to HR MDS or CMML, or low-blast AML when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine delays time to PD, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death when compared with single-agent azacitidine.
- To determine whether the combination of pevonedistat and azacitidine maintains overall health status/quality of life and fatigue domain scores as measured by the PRO instrument EORTC QLQ-C30 when compared with single-agent azacitidine.
- To collect plasma concentration-time data for pevonedistat to contribute to future population PK analyses of pevonedistat.
- To compare ORR, EFS, and OS in patients who have *TP53* mutations, 17p deletions, and/or are determined to be in an adverse cytogenetic risk group at Baseline, across treatment arms.

5.1.4 Safety Objective

The safety objective is:

- To evaluate the safety of the combination of pevonedistat and azacitidine when compared with single-agent azacitidine.

5.1.5 Exploratory Objectives

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[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is:

- EFS: time from randomization to the date of an EFS event (defined as death or transformation to AML in patients with MDS or CMML, whichever occurs first, and defined as death in patients with low-blast AML).

5.2.2 Key Secondary Endpoint

The key secondary endpoint is:

- OS.

5.2.3 Other Secondary Endpoints

Other secondary endpoints are:

- Six-month and 1-year survival rates.
- Thirty-day and 60-day survival rates.
- Time to AML transformation in patients with HR MDS, patients with HR CMML, and patients with HR MDS/CMML.
- Rate of CR (CR in patients with HR MDS or CMML, or low-blast AML), CR+CRi in patients with low-blast AML, CR+marrow CR (in patients with HR MDS or CMML), CR+PR+HI (in patients with HR MDS or CMML), CR+marrow CR+PR (in patients with HR MDS or CMML), CR+marrow CR+PR+HI (in patients with HR MDS or CMML), overall response, overall response by Cycle 6, and overall response 2. Overall response in patients with HR MDS or CMML is defined as CR+PR; overall response in patients with low-blast AML is defined as CR+CRi+PR. Overall response 2 in patients with HR MDS or CMML is defined as CR+PR+HI; overall response 2 in patients with low-blast AML is defined as CR+CRi+PR.
- Duration of CR (CR for HR MDS or CMML, or low-blast AML), CR+CRi for low-blast AML, overall response (CR+PR for HR MDS or CMML, CR+CRi+PR for low-blast AML), and overall response 2 (CR+PR+HI for HR MDS or CMML, CR+CRi+PR for low-blast AML).
- Rates of RBC and platelet transfusion independence.
- Duration of RBC transfusion independence, platelet transfusion independence, and platelet and RBC transfusion independence.
- Time to first CR or PR or CRi (for patients with low-blast AML).
- Rates of HI in patients with HR MDS, patients with HR MDS/CMML, and patients with HR CMML.
- Patients who have inpatient hospital admission(s) related to HR MDS or CMML (collected through transformation to AML or until initiation of subsequent therapy, whichever occurs first) or low-blast AML (collected through initiation of subsequent therapy).
- Time to PD, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death.
- HRQOL assessed using the EORTC QLQ-C30.
- Plasma concentration-time data for pevonedistat.
- ORR, EFS, and OS in patients who have *TP53* mutations, 17p deletions, and/or are determined to be in an adverse cytogenetic risk group in both treatment arms.

5.2.4 Safety Endpoints

The safety endpoints are:

- AEs.
- SAEs.
- Results of clinical laboratory tests.
- ECOG PS.

5.2.5 Exploratory Endpoints

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6.0 STUDY DESIGN

6.1 Overview of Study Design

This study is a multicenter, global, randomized, controlled, open-label, phase 3 clinical study of the combination of pevonedistat and azacitidine versus single-agent azacitidine administered in patients with HR MDS or CMML, or low-blast AML (see Section 7.1, inclusion criteria 2 and 3 for definitions) who have not previously received chemotherapy or other antineoplastic agents including HMAs such as decitabine or azacitidine. Patients with nonproliferative CMML (ie, WBC <13,000/µL) are included because these patients were also included in both randomized studies of azacitidine conducted in the US and EU and were shown to have response rates similar to MDS patients.

General eligibility may be assessed before the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events (SOE) (Appendix C), formal screening will occur during the Screening period, which may last up to 28 days before randomization. The sponsor's project clinician (or designee) will confirm patient eligibility before randomization by the investigator.

It is expected that approximately 450 patients, including at least 350 patients with HR MDS or CMML and at least 100 patients with low-blast AML, will be enrolled in this study. At enrollment, patients with HR MDS or CMML, or low-blast AML will be randomized at a 1:1 ratio to receive study drug (either single-agent azacitidine or the combination of pevonedistat and azacitidine) in 28-day treatment cycles. All patients will be stratified into 4 categories: low-blast AML, IPSS-R risk groups of very high, high, or intermediate for MDS or CMML [1]. Note that patients with HR MDS or CMML with indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points, ie, intermediate, for determining overall Prognostic Risk Category/Score; see Section 9.4.4. All patients will receive azacitidine (75 mg/m^2 [IV or SC]) on Days 1 through 5, Day 8, and Day 9. Patients randomized to the combination arm will also receive pevonedistat (20 mg/m^2 via 60 ([±10]-minute infusion) on Days 1, 3, and 5. Modifications to the dose and schedule may be allowed as detailed in the SOE (Appendix C) and Section 8.1.

Patients, including those who achieve a CR, may receive study treatment until they experience unacceptable toxicity, relapse, transformation to AML, or PD as defined in Section 9.4.20. Patients may be allowed to continue study treatment (either treatment arm) if they meet the criteria for PD based only on bone marrow blast count (without AML transformation in patients with HR MDS or CMML) if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment. Patients may choose to discontinue therapy at any time.

Patients will attend the End-of-Treatment (EOT) visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner.

Following the EOT visit, patients with HR MDS or CMML will enter EFS follow-up, if their disease has not transformed to AML. Patients will have monthly assessments to include physical

exam, clinical blood tests, HRQOL assessments, hospitalization assessment, and disease assessment as outlined in the SOE (Appendix C). Patients who discontinue study treatment without evidence of progression (ie, PD or transformation to AML) will have a bone marrow aspirate and hematology tests (see Table 9.d) sent to the central laboratory at time of suspected progression (see SOE [Appendix C] and Table A). Patients will continue monthly EFS follow-up study visits until their disease transforms to AML or they start subsequent therapy (see Study Diagram in Appendix B). Patients who have started subsequent therapy will have EFS follow-up but will not be required to have monthly visits; at the time of suspected transformation to AML they will have a bone marrow aspirate and hematology tests (specimens sent to central laboratory).

Following the EOT visit, patients with low-blast AML will enter response follow-up, if they have no evidence of PD and they have not started subsequent therapy. Patients will have monthly assessments to include physical exam, clinical blood tests, HRQOL assessments, hospitalization assessment, and disease assessment as outlined in the SOE (Appendix C). Patients who discontinue study treatment while not in CR and without evidence of PD will have a bone marrow aspirate and hematology tests sent to the central laboratory at the time of suspected PD. Patients who discontinue treatment while in CR will also have a bone marrow aspirate and hematology tests performed at the time of suspected relapse sent to the central laboratory (see Table A). Patients will continue monthly response follow-up visits, until they relapse from CR or meet the criteria for PD (see Study Diagram in Appendix B).

Following the EFS and response follow-up visits, or the EOT visit (for patients with HR MDS or CMML who discontinue study treatment because of transformation to AML, or patients with low-blast AML who discontinue study treatment because of PD), patients will enter OS follow-up and will be contacted every 3 months until death to document subsequent therapies and survival status (see Study Diagram in Appendix B).

Disease response assessments for all HR MDS and CMML patients will be based on the Modified International Working Group (IWG) response criteria for MDS [2] as detailed in Section 9.4.20. Disease response assessments for patients with low-blast AML will be based on the Revised Recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia as detailed in Section 9.4.20 [3]. Formal disease assessments for study endpoints will be determined based on local bone marrow aspirate blast counts (blast counts from the bone biopsy may be used in the event the aspirate sample is inadequate and a biopsy was done), clinical laboratory evaluations performed at a central laboratory (local laboratory results may be used for time-sensitive clinical decisions), and local transfusion data.

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

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

Bone marrow aspirates will be obtained at Screening and at additional time points described in Table A and in Section 9.4.24 for assessing response and/or for translational research purposes. Samples will be collected and analyzed from patients in both treatment arms and sent to a central laboratory. Bone marrow aspirates collected at Screening will be used to analyze tumor cytogenetics, baseline somatic mutations, and other molecular characteristics such as gene expression profile and epigenetic status. Bone marrow aspirates collected at the specified time points during treatment and/or at relapse will be used to evaluate depth and duration of response by following parameters such as residual tumor cells, residual mutation load, and changes in epigenetic modifications. Such analysis will also be used to identify treatment-emergent mutations. Developing potential biomarkers of pevonedistat-mediated activity may require analysis of the data from this study in combination with data from other clinical studies of pevonedistat.

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

AEs and ECOG PS will be assessed, and ECGs, clinical laboratory values, and vital signs will be obtained, to evaluate the safety and tolerability of the study drug treatments. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010 [4]. Dose modification guidelines are presented in Section 8.3.

PROs will be evaluated using the EORTC QLQ-C30, version 3.0, and EQ-5D-5L questionnaires.

6.2 Number of Patients

Approximately 450 patients (randomized in a 1:1 ratio), including at least 350 patients with HR MDS or CMML and at least 100 patients with low-blast AML, will be enrolled in this study from approximately 120 study centers globally. Enrollment is defined as when the patient is randomized onto study treatment. Enrollment will be managed to ensure an appropriate distribution of patient with HR MDS or CMML, and low-blast AML.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients, including those who achieve a CR, may receive study treatment until they experience unacceptable toxicity, relapse, transformation to AML (for patients with HR MDS or CMML), PD (for patients with low-blast AML), the sponsor terminates the study, or discontinuation for any other reason outlined in Section 9.7.

After discontinuing study treatment, patients will be followed until death for survival status, subsequent therapy, and disease status (for patients with HR MDS or CMML).

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

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The study will be considered complete after the final analysis (FA) for OS has been completed or the study has been terminated by the sponsor. The estimated time frame for study completion is approximately 65 months after the first patient is enrolled. Patients who are still receiving study treatment and continuing to derive clinical benefit may continue to receive pevonedistat at the discretion of the sponsor; the continuation of treatment may occur in a manner other than the study protocol and according to local regulations.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame (a)
Primary:		
• EFS	The time from randomization to the occurrence of an event. For patients with HR MDS/CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death.	Up to 6 years
Secondary:		
• OS	The time from randomization to death from any cause.	Up to 6 years
Other Secondary:		Up to 6 years
• 6 month and 1 year survival rates	Kaplan-Meier (K-M) estimates for 6 month and 1 year survival rates.	
• 30-and 60-day mortality rates	The proportion of patients who survive at most 30/60 days from the first dose of study drug.	
• Time to AML transformation	The time from randomization to documented AML transformation.	
• Rate of CR, CR+CRi, CR+marrow CR, CR+PR+HI, CR+marrow CR+PR,CR+ marrow CR+PR+HI, overall response, overall response by Cycle 6, and overall response 2	As evaluated by the independent review committee (IRC).	

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame (a)
• Duration of CR, CR+CRi, overall response, and overall response 2	CR, CR or PR, CR or PR or HI for HR MDS or CMML; CR or CRi, CR or CRi or PR for low-blast AML to first documentation of PD or transformation to AML.	
• Rate of RBCs and/or platelet-transfusion independence	Rate of RBCs and/or platelet-transfusion independence is defined as number of patients who become RBCs and/or platelet transfusion independent divided by the number of patients who are RBCs and/or platelet transfusion dependent at Baseline.	
• Duration of RBC transfusion independence, platelet transfusion independence, and platelet and RBC transfusion independence	The time from the first established RBC and/or platelet transfusion independence to the subsequent first RBC and/or platelet transfusion.	
• Time to first CR or PR or CRi	The time from randomization to first documented CR or PR or CRi, whichever occurs first.	
• Rates of HI (see Table 9.i)	Rates of HI as evaluated by IRC.	
• Percent of patients who have inpatient hospital admission(s) related to HR MDS or CMML, or low-blast AML	The ratio of the number of patients who have hospital admission(s) related to HR MDS or CMML, or low-blast AML over the number of patients in the intent-to-treat (ITT) population per treatment arm.	
• Time to PD, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death	The time from randomization until PD, or relapse after CR or PR, or death due to any cause, whichever occurs first.	
• HRQOL	Measured by domains from EORTC QLQ-C30, EORTC supplemental items, and EQ-5D-5L.	
• Plasma concentration-time data for pevonedistat	Pevonedistat concentration at prespecified collection time.	

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame (a)
• Determine ORR, EFS and OS in patients that have *TP53* mutations, 17p deletions, and/or are determined to be in an adverse cytogenetic risk group in both treatment arms	Similar definition of ORR, EFS and OS as above applied to patients that have *TP53* mutations, 17p deletions, and/or are determined to be in an adverse cytogenetic risk group in both treatment arms.	Up to 6 years

AML= acute myelogenous leukemia, CMML= chronic myelomonocytic leukemia, CR=complete remission, EFS=event-free survival, EORTC QLQ-C30= European Organisation for the Research and Treatment of Cancer Core Quality of Life Questionnaire, EQ-5D-5L= EuroQoL 5 dimensions 5 levels (a quality of life questionnaire of the "EuroQoL Group Association" that was expanded to a 5-level instrument), HI= hematologic improvement, HR MDS= higher-risk myelodysplastic syndromes, HRQOL= health-related quality of life, ORR=overall response rate, OS=overall survival, PD=progressive disease, PR=partial remission, RBC=red blood cell.
(a) Time to last assessment for that endpoint across the entire study.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 63 months.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.
2. Morphologically confirmed diagnosis of MDS or nonproliferative CMML (ie, with WBC <13,000/μL) or low-blast AML based on 1 of the following:

   FAB Classifications [5]:

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

   OR

   WHO Classifications [6]:

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

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

3. All patients with MDS or CMML must also have one of the following Prognostic Risk Categories, based on the IPSS-R [1]:
   - Very high (>6 points).
   - High (>4.5-6 points).
   - Intermediate (>3-4.5 points): a patient determined to be in the Intermediate Prognostic Risk Category is only allowable in the setting of ≥5% bone marrow myeloblasts.
4. ECOG PS of 0, 1, or 2 (see Appendix F).
5. Patients with AML (20%-30% blasts) must have a TRM score ≥4 for intensive, induction chemotherapy) as calculated using the simplified model described by Walter and coworkers [7]; see Appendix A.

   Calculation of TRM score:
   - 0 for (age <61 years), +2 for (age 61-70 years), +4 for (age ≥71 years).
   - + 0 for (PS=0), +2 for (PS=1), +4 for (PS >1).
   - + 0 for (platelets <50), +1 for (platelets ≥50).
6. Female patients who:
   - Are postmenopausal (see Appendix G) for at least 1 year before the Screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method (see Appendix H), at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus five half-lives) after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

7. Ability to undergo the study-required bone marrow sample collection procedures.
8. Suitable venous access for the study-required blood sampling (ie, including PK and pharmacodynamic sampling).
9. Clinical laboratory values within the following parameters (repeat within 3 days before the first dose of study drug if laboratory values used for randomization were obtained more than 3 days before the first dose of study drug):
    - Albumin >2.7 g/dL.
    - Total bilirubin ≤ the upper limit of the normal range (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5×ULN of the direct bilirubin.
    - ALT and AST ≤2.5×ULN.
    - Creatinine clearance ≥50 mL/min (see Appendix I).
    - Hemoglobin >8 g/dL. Patients may be transfused to achieve this value. Elevated indirect bilirubin due to posttransfusion hemolysis is allowed.
10. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7.2 Exclusion Criteria

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

1. Previous treatment for HR MDS or CMML, or low-blast AML with chemotherapy or other antineoplastic agents including HMAs such as decitabine or azacitidine. Previous treatment is permitted with hydroxyurea and with lenalidomide, except that lenalidomide may not be given within 8 weeks before the first dose of study drug.
2. Acute promyelocytic leukemia as diagnosed by morphologic examination of bone marrow, by fluorescent in situ hybridization or cytogenetics of peripheral blood or bone marrow, or by other accepted analysis.

3. Patients with AML with a WBC count >50,000/ μL. Patients who are cytoreduced with leukapheresis or with hydroxyurea may be enrolled if they meet the eligibility criteria.
4. Eligible for intensive chemotherapy and/or allogeneic stem cell transplantation. The reason a patient is not eligible for intensive chemotherapy and/or allogeneic stem cell transplantation may consist of one or more of the following factors:
    - Age >75.
    - Comorbidities.
    - Inability to tolerate intensive chemotherapy (eg, patients with AML with 20%-30% blasts and TRM ≥4).
    - Physician decision (eg, lack of available stem cell donor).

    The reason a patient is not eligible should be documented in the electronic case report form (eCRF).
5. Patients with either clinical evidence of or history of central nervous system involvement by AML.
6. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures or could limit expected patient survival to less than 6 months.
7. Treatment with any investigational products or participation in any interventional studies within 14 days before the first dose of any study drug.
8. Known hypersensitivity to pevonedistat or its excipients.
9. Known hypersensitivity to azacitidine or its excipients.
10. Active uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, or septicemia.
11. Major surgery within 14 days before first dose or a scheduled surgery during study period; insertion of a venous access device (eg, catheter, port) is not considered major surgery.
12. Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone resection.
13. Life-threatening illness unrelated to cancer.
14. Prothrombin time (PT) or aPTT >1.5×ULN or active uncontrolled coagulopathy or bleeding disorder. Patients therapeutically anticoagulated with warfarin, direct thrombin inhibitors, direct factor Xa inhibitors, or heparin are excluded from enrollment.
15. Known human immunodeficiency virus (HIV) seropositive.

16. Known hepatitis B surface antigen seropositive, or known or suspected active hepatitis C infection. Note: Patients who have isolated positive hepatitis B core antibody (ie, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load.
17. Known hepatic cirrhosis or severe preexisting hepatic impairment.
18. Known cardiopulmonary disease defined as unstable angina, clinically significant arrhythmia, congestive heart failure (New York Heart Association Class III or IV; see Appendix J), and/or myocardial infarction within 6 months before first dose, or severe pulmonary hypertension. As an example, well-controlled atrial fibrillation would not be an exclusion whereas uncontrolled atrial fibrillation would be an exclusion.
19. Treatment with strong CYP3A inducers (see Appendix K) within 14 days before the first dose of pevonedistat.
20. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.
21. Female patients who intend to donate eggs (ova) during the course of this study or for 4 months after receiving their last dose of study drug(s).
22. Male patients who intend to donate sperm or father a child during the course of this study or for 6 months after receiving their last dose of study drug(s).

8.0 STUDY DRUG

8.1 Study Drug Administration

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

The first dose of study drug must be administered within 5 days of randomization on study. It is strongly recommended that dosing for both treatment arms occur on the days specified (ie, azacitidine dosing on Days 1-5, 8, and 9; pevonedistat dosing on Days 1, 3, and 5). However, dosing of either drug may be delayed for safety reasons or other unavoidable circumstances (eg, weather affecting clinic accessibility). If pevonedistat dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained. In each cycle, a maximum of 3 doses of pevonedistat and 7 doses azacitidine (as applicable) should not be exceeded. For the combination arm, pevonedistat and azacitidine should always be administered on the same day (eg, instead of pevonedistat dosing on Days 1, 3, and 5, it would be acceptable to dose on Days 1, 5, and 8). If dosing is adjusted, study procedures should be performed on the actual day of dosing. Actual start and stop times of the study drug administration, should be recorded accurately.

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

example in Appendix M) on Cycle 1 Day 1, and on Day 1 of subsequent cycles if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

8.1.1 All Patients: Azacitidine Dosing

All patients will receive azacitidine (75 mg/m^2 [IV or SC, per investigator's choice]) on Days 1 through 5, Day 8, and Day 9 of each treatment cycle. To the extent possible, the investigator should maintain the same route of administration of azacitidine for the patient during the study. However, the investigator, without approval of the sponsor's project clinician, may choose to switch the route of azacitidine administration at any time based on clinical or logistic reasons (eg, loss of IV access or occurrence of local irritation with SC administration). Please see the most recent VIDAZA (azacitidine) USPI [44] or EU SmPC [76], for details on azacitidine administration.

8.1.2 Additional Instructions for the Combination Arm: Pevonedistat Plus Azacitidine Dosing

Patients assigned to the Combination Pevonedistat Plus Azacitidine Arm will receive azacitidine as described in Section 8.1.1 and will also receive pevonedistat (20 mg/m^2) via 60 (±10) minute infusion on Days 1, 3, and 5. All doses must be taken as outlined in the SOE (Appendix C).

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

The entire content of the pevonedistat IV bag will be infused at a constant rate over 60 (±10) minutes. The start and end time of IV infusion should be recorded accurately, particularly in Cycle 1, when PK assessments are performed. To ensure that all the pevonedistat is administered, the infusion line will be flushed with 0.9% saline or 5% dextrose immediately after administration. The volume used for line flushing is not considered a part of the volume of the pevonedistat IV bag to be documented.

On Days 1, 3, and 5, when both study drugs are administered, azacitidine will be administered first followed by pevonedistat. The infusion of pevonedistat will begin between 15 and 60 minutes after completion of administration of SC azacitidine, and between 30 and 60 minutes after completion of administration of IV azacitidine

8.2 Reference/Control Therapy: Azacitidine

Azacitidine is a chemical analogue of cytidine that is widely used for the treatment of patients with AML. A phase 3, randomized, open-label, international study compared azacitidine (75 mg/m^2 SC daily for 7 days, every 28 days) with investigator-selected CCRs (eg, best supportive care,

low-dose cytarabine, or intensive chemotherapy) in 358 patients with HR MDS as defined at that time [16].

Approximately one third (n=113) of the patients in this study had RAEB-t (20%-30% bone marrow blasts); under the 2008 WHO-revised criteria, RAEB-t is now defined as AML [6]. A subanalysis of the study compared the relative efficacy and safety of azacitidine versus CCR in this patient subgroup (median age 70 years) [78]. Of these 113 patients with WHO-defined AML, 86% were considered unfit for intensive chemotherapy. Two-year OS rates were higher with azacitidine versus CCR in the patients considered unfit for intensive chemotherapy (51% vs 13%, respectively, p=0.0003). In addition, azacitidine was associated with fewer total days in the hospital (26.0 vs 50.9 days per patient-year; relative risk=0.48; 95% CI 0.44-0.52; p<0.0001) than CCR. In patients with unfavorable cytogenetics, median OS in the azacitidine (n=14) and CCR (n=13) groups was 12.3 and 5.3 months, respectively (hazard ratio=0.66; 95% CI 0.26-1.68; p=0.38), whereas the 2-year OS rate was 38% for azacitidine, with no patients surviving more than 20 months in the CCR group (p=0.01) [78].

In a randomized phase 3 trial of azacitidine versus CCR in older patients with newly diagnosed AML, the median OS with azacitidine was 10.4 months, a 3.8 month (58%) increase over CCR. One-year survival with azacitidine was 47%, a 36% increase over CCR. Although the study did not reach statistical significance for its primary endpoint of OS (p=0.08), azacitidine demonstrated a clinically meaningful improvement. A sensitivity analysis of OS censoring at subsequent AML therapy demonstrated a statistically significant benefit for azacitidine versus CCR (12.1 vs 6.9 months, respectively; p=0.0147) [79].

8.3 Dose Modification Guidelines

8.3.1 Criteria for Retreatment and Dose Delays

Retreatment Within a Cycle

If dosing of either drug is delayed for safety reasons, retreatment may be resumed upon resolution of the safety condition to ≤Grade 1. For pevonedistat, a minimum of 1 full calendar day between any 2 doses should be maintained. In each cycle, a maximum of 3 doses of pevonedistat and 7 doses azacitidine (as applicable) should not be exceeded. If azacitidine is held for whatever reason, it may be resumed to complete a full treatment course as long as the full 7 doses are completed within the first 14 days of the cycle.

If dosing is interrupted within a cycle because of drug-related toxicity, and if the investigator and the sponsor's project clinician (or designee) agree that it is in the patient's interest to continue therapy with the study drug(s), then after recovery of the toxicity or toxicities in question to ≤Grade 1 or to the patient's baseline values, the dose of study drug may be reduced. For toxicity not related to drug (eg, disease-related toxicity), although a similar dose reduction is permitted, in general it is discouraged. If the reduced dose is well tolerated and the toxicity leading to dose reduction was ≤Grade 3, has resolved, and does not re-occur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor's project clinician (or designee). For specific guidelines on azacitidine and pevonedistat dose reductions, see Sections 8.3.2 and 8.3.3.

Initiation of a New Cycle

Treatment with study drugs will be repeated every 28 days. It is strongly recommended that dosing for both treatment arms occur on the days specified. However, the initiation of a new cycle may be delayed for safety reasons or other unavoidable circumstances (eg, weather affecting clinic accessibility). For therapy to resume, nonhematologic toxicity considered related to treatment with study drugs must have resolved to ≤Grade 1, to the patient's baseline values, or to a level considered acceptable by the investigator after discussion with sponsor's project clinician (or designee). Criteria for dosing in a new cycle related to hematologic toxicities are detailed for azacitidine in Section 8.3.2.1 and for pevonedistat in Section 8.3.2.2.

If a patient fails to meet the criteria for retreatment, initiation of the next cycle of treatment may be delayed for up to 2 weeks. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. A dose reduction (as detailed in Sections 8.3.2 and 8.3.3) would be triggered if treatment is delayed for >2 weeks because of incomplete recovery from treatment-related toxicity. If the reduced dose is well tolerated and the toxicity leading to dose reduction was ≤Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor's project clinician (or designee).

Discontinuation of Treatment due to Study Drug–Related Toxicity

Study drug may be held for up to 6 weeks (42 days) because of study drug–related toxicity before a patient must be removed from protocol therapy.

8.3.2 Dose Modification for Hematologic Toxicities

8.3.2.1 Azacitidine

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

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

- Absolute neutrophil count (ANC) is <500/µL. For patients with disease-related neutropenia, physician discretion may be used to initiate therapy with ANC ≥50% of baseline (baseline from the start of the previous cycle). In general, the use of growth factors should be restricted. However, to avoid dose delay, patients who experience Grade 4 neutropenia (ANC <500/µL) with or without fever may receive G-CSF or granulocyte macrophage colony-stimulating factor (GM-CSF) between days 28 to 42 days of azacitidine monotherapy or combination after discussion and agreement with the sponsor's project clinician (or designee). Any use of growth factors will be documented in the eCRF. Patients who receive myeloid growth factors will not be included in assessment of neutrophil response during that cycle.

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

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

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

8.3.2.2 Pevonedistat

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

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

8.3.3 Dose Modification for Nonhematologic Toxicities

8.3.3.1 Azacitidine

Azacitidine Dose Adjustment Based on Renal Function and Serum Electrolytes

For renal toxicities, specifically elevated creatinine >Grade 1, azacitidine should be reduced in accordance with the prescribing information [44] and/or institutional guidelines. Similarly, if unexplained elevations in serum creatinine or blood urea nitrogen (BUN) occur, the next cycle should be delayed until values return to normal or baseline values, and the dose should be reduced by 50% on the next treatment course.

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

8.3.3.2 Pevonedistat

Pevonedistat Dose Adjustment Based on Serum Transaminases and Total Bilirubin

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

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

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

Pevonedistat Dose Adjustment Based on Hypophosphatemia

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

Pevonedistat Dose Adjustment for Other Toxicities

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

8.4 Excluded Concomitant Medications and Procedures

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

The effect of rifampin, a strong CYP3A inducer, on pevonedistat PK was evaluated in Study P1015. The geometric mean AUC from time 0 to infinity of pevonedistat in the presence of rifampin was 79% of that in the absence of rifampin (90% CI: 69.2%, 90.2%). The result indicated that co-administration of rifampin did not result in clinically meaningful alteration of pevonedistat systemic exposures in the context of 28% of inter-individual variability in pevonedistat clearance. Based on these findings, CYP3A inducers are no longer included in the list of excluded concomitant medications.

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

Medications that are generally excluded but are allowed with certain exceptions are listed in Table 8.a.

Table 8.a Concomitant Medications Excluded While Receiving Study Treatment (Single Agent Azacitidine or Combination Pevonedistat Plus Azacitidine)

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	May be used judiciously but should not exceed a dose of 2 g in 24 hours.
Systemic antineoplastic therapy, except for hydroxyurea	Hydroxyurea dosing during the study treatment phase may be adjusted to control the level of circulating blast counts to no lower than 10,000/µL while on study treatment. The dosing of hydroxyurea and changes to dosing of hydroxyurea must be recorded.
Any investigational agent, other than pevonedistat in the combination arm, for MDS, CMML, or low-blast AML, or commercially available agents used in MDS, CMML, or low-blast AML, including androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]	

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

8.5 Permitted Concomitant Medications and Procedures

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

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

Therapy	Comment
Antiplatelet agents (eg, aspirin, clopidogrel) and anticoagulants	May be used in patients who develop a thrombosis while on study. Note that patients with active uncontrolled coagulopathy or who are therapeutically anticoagulated with warfarin, direct thrombin inhibitors, direct Xa inhibitors or heparin are excluded from enrollment as per Section 7.2.
Antiemetics for azacitidine	May be administered according to institutional guidelines.
Myeloid growth factors (eg, G-CSF, GM-CSF)	In general, the use of myeloid growth factors is discouraged and should be restricted. For patients in CR, CRi, or marrow CR, growth factors may be used in specific circumstances after discussion with the project clinician or designee. Use of growth factors may also be used in patients with Grade 3 or Grade 4 febrile neutropenia after discussion and agreement with the project clinician or designee. Additionally to avoid dose delays, patients who experience Grade 4 neutropenia (ANC <500/μL) with or without fever may receive G-CSF or GM-CSF between days 28-42 days of azacitidine monotherapy or combination after discussion and agreement with the sponsor's project clinician (or designee). Patients who receive myeloid growth factors will not be included in assessment of neutrophil response.
Platelet transfusion	Permitted as medically necessary per institutional guidelines (eg, for platelets <10,000/μL in the absence of clinical bleeding); see Section 8.7.
Red blood cell transfusion	To be considered for all patients with anemia, especially those with hemoglobin values ≤8 g/dL; see Section 8.7.

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

8.6 Precautions and Restrictions

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

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

Refer to the package insert for VIDAZA USPI [44] or EU SmPC [76], for precautions and restrictions related to azacitidine use.

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

Female patients must meet 1 of the following:

- Postmenopausal (see definition in Appendix G) for at least 1 year before the Screening visit, OR

- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through 4 months after the last dose of study drug (whichever is longer), OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

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

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus five half-lives) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients must agree to not donate sperm or father a child during the course of this study or for 6 months after receiving their last dose of study drug(s).

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

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

8.7 Management of Clinical Events

8.7.1 Azacitidine

The most common adverse drug reactions for azacitidine are described in Section 4.6.1. For the single-agent azacitidine treatment arm, refer to the VIDAZA USPI [44] or EU SmPC [76], as applicable, for details regarding the management of clinical events attributed to azacitidine.

Guidance for Management of Necrotizing Fasciitis

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with azacitidine. Azacitidine therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated per institutional guidelines.

8.7.2 Combination Pevonedistat Plus Azacitidine

Common AEs reported for patients receiving the combination of pevonedistat and azacitidine are listed in Section 4.6.2. Also see the most recent IB. For the Combination Pevonedistat Plus Azacitidine Arm, follow the guidance in the following subsections of this protocol.

Guidance for Clinical Assessment and Management of Hemodynamic Compromise

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

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

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

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

Guidance Management of Leukostasis

Pevonedistat treatment should be withheld for patients who develop symptoms of leukostasis (see Section 8.3.2.2). Treatment may include leukapheresis and hydroxyurea administration, per institutional guidelines. When the WBC of the patient is <50,000/μL and symptoms are improved, pevonedistat treatment may be restarted after consulting with the sponsor's project clinician (or designee). Azacitidine treatment may continue as clinically indicated.

Guidance for Management of Extravasation

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

8.8 Blinding and Unblinding

This is an open-label study. Takeda's staff or its designee that is directly involved in the study will be blinded to the treatment assignment of patients in the trial. The independent review committee (IRC) will be blinded to treatment assignments.

8.9 Description of Investigational Agents

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

8.9.1 Azacitidine

Azacitidine may be supplied by the site from commercial sources, depending on regional availability. Commercially available azacitidine is supplied as lyophilized powder in 100-mg single-use vials. Refer to the Study/Pharmacy Manual and the VIDAZA USPI [44] or EU SmPC [76], as applicable, for additional information regarding azacitidine.

8.9.2 Pevonedistat

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

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

Each Pevonedistat Concentrate for Solution for Infusion vial contains 50 mg Pevonedistat, as free base, formulated with the following excipients: CCI [redacted]

Details are available in the IB.

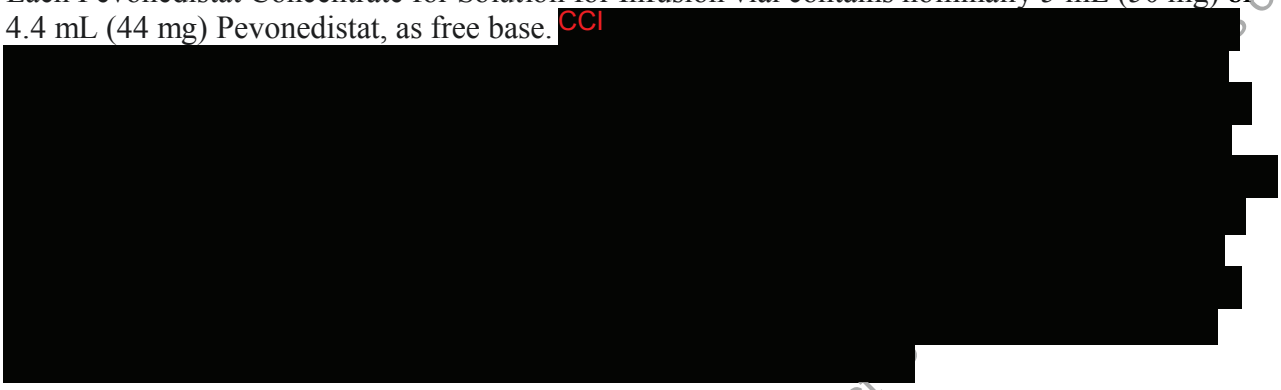
8.10 Preparation, Reconstitution, and Dispensation

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

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

If the drug product vial is not to be used within the 6-hour timeframe, the vial should be returned to storage. Each vial is for single use only.

Each Pevonedistat Concentrate for Solution for Infusion vial contains nominally 5 mL (50 mg) or 4.4 mL (44 mg) Pevonedistat, as free base. CCI



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

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

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

Instructions for the preparation, reconstitution, and dispensation of azacitidine are provided in the VIDAZA USPI [44] or EU SmPC [76].

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

8.11 Packaging and Labeling

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

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

8.12 Storage, Handling, and Accountability

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

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

Details of the storage and handling of azacitidine are provided in the VIDAZA USPI [44] or EU SmPC [76].

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

8.13 Other Protocol-Specified Materials

Refer to the Pharmacy Manual.

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

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

9.2 Arrangements for Recruitment of Patients

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

9.3 Treatment Group Assignments

Patient eligibility will be established before randomization into the study as patients will not be permitted to re-enroll. Confirmation of patient eligibility by the sponsor's project clinician (or designee) following review and approval of a Patient Eligibility Checklist is required before randomization. A centralized randomization and stratification using an interactive web response system (IWRS) will be used. Patients will be randomized strictly sequentially at a center as they become eligible for randomization and will be stratified as detailed in Section 13.2. The study drug regimen must be initiated within 5 days of randomization on study. If a patient discontinues from the study, his/her randomization code will not be reused, and the patient will not be allowed to re-enter the study.

9.4 Study Procedures

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

Nonessential protocol visits that do not require on-site sample collection and assessment may be completed via telemedicine (video or phone conversation between the patient and the treating

physician, if allowed per Health Authorities, privacy laws, and institutional and local guidelines) in situations where a site visit cannot be conducted, such as in a COVID-19 pandemic.

9.4.1 Informed Consent

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

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

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

9.4.2 Inclusion/Exclusion Confirmation

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

9.4.3 Patient Demographics

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

9.4.4 Medical History and IPSS-R Risk Categorization

During Screening, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's MDS, CMML, or low-blast AML (see inclusion criteria 2 and 3, Section 7.1, for definitions), including an assessment of bone marrow morphology (see Section 9.4.24 for additional details on bone marrow sample collection and evaluation). Information regarding any prior therapy for MDS, CMML, or low-blast AML, including start and stop dates of each therapeutic agent and response to therapy, will be collected in the eCRF. In addition, all blood transfusions related to MDS, CMML, or low-blast AML that the patient received within 8 weeks before randomization will be recorded to document baseline transfusion dependence.

For patients with MDS or CMML (but not for patients with low-blast AML), screening assessments must include risk categorization (for both MDS and CMML patients) according to the IPSS-R [1]. Source documents supporting the prognostic risk category determination may be requested with the Patient Eligibility Checklist for review by the sponsor before randomization (see Section 9.4.2).

The IPSS-R Prognostic Score values based on specific criteria are provided in Table 9.a and the IPSS-R cytogenetic risk groups are provided in Table 9.b. Cytogenetic risk groups and bone marrow blast percentages will be based upon results from the local laboratory, while clinical lab values (hemoglobin, platelets and ANC) should be from the central laboratory results. Criteria and score values from these tables are used to determine the overall risk category as listed in Table 9.c. These 3 tables have been adapted from: www.mds-foundation.org/ipss-r-calculator/ (accessed 05 January 2015), based on Greenberg et al., 2012 [1].

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

Table 9.a IPSS-R Prognostic Score Values

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

Source: Greenberg et al., 2012 [1].
BM=bone marrow; ANC=absolute neutrophil count; IPSS-R=Revised International Prognostic Scoring System.
(a) Patients with indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points (ie, intermediate) for determining overall Prognostic Risk Category/Score.

Table 9.b IPSS-R Cytogenetic Risk Groups

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

Sources: Greenberg et al., 2012 [1] and Schanz J et al., 2012 [80].
IPSS-R=Revised International Prognostic Scoring System.

Table 9.c IPSS-R Prognostic Risk Categories/Scores

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

Source: Greenberg et al., 2012 [1].
IPSS-R=Revised International Prognostic Scoring System.

Risk status among patients with AML (favorable, intermediate, and poor risk categories), also have been defined according to cytogenetics and molecular abnormalities. For example, patients with *TP53* mutations are classified as poor risk AML [48]. Cytogenetics, mutation analysis and molecular analysis will be done to assess these factors.

9.4.5 Modified Charlson Comorbidity Index Assessment

Patients will be assessed during Screening using the Modified Charlson Comorbidity Index (refer to Appendix L).

9.4.6 Physical Examination

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

9.4.7 Patient Height

Height will be measured only during Screening.

9.4.8 Patient Weight

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

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

9.4.9 ECOG PS

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

9.4.10 Vital Signs

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

9.4.11 Pregnancy Test

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

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

9.4.12 PROs

To compare the impact of treatment between the 2 treatment arms in this study, patient-reported HRQOL will be assessed by 2 instruments: EORTC QLQ-C30, version 3.0, and EQ-5D-5L.

The patient should be given the paper version of the questionnaires to complete at the scheduled visit before other clinical assessments are conducted. The questionnaires should be completed in the language most familiar to the respondent, at the scheduled visit, before the patient sees the investigator for clinical assessments. The patient should be given sufficient space and time to complete the questionnaires. The patient should complete the questionnaires on their own without any assistance from site staff or a caregiver. The questionnaires are intended to be self-reported and should not be interviewer-administered.

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

EORTC QLQ-C30

The EORTC QLQ C30 [72] was designated to assess HRQOL in a wide range of cancer patient populations and contains 30 items which incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties), and a global quality of life/health status scale. Most of the 30 items have 4 response levels (not at all, a little, quite a bit, and very much), with 2 questions relying on a 7-point numeric rating scale. Supplemental items on symptoms (7 items) and functional impacts (3 items) from the EORTC item bank will also be included. The supplemental 10 items have 4 response levels (not at all, a little, quite a bit, and very

much). Raw scores are converted into scale scores ranging from 0 to 100. For the functional scales and the global health status scale, higher scores represent better HRQOL; whereas for the symptom scales lower scores represent better HRQOL. All items in this questionnaire relate to a recall period of 1 week.

EQ-5D-5L

The EQ-5D-5L is a self-administered, preference-based measure of health status. EQ-5D-5L includes 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and 5 response levels for each domain (no problems, slight problems, moderate problems, severe problems, and extreme problems). Patients are asked to indicate their health state by selecting the most appropriate level of severity on each of the 5 dimensions. Patient responses to the 5 dimensions of the EQ-5D-5L represent the patient's health state that is transformed to a utility score using preferably country-specific value sets. There is also a visual analogue scale used by respondents to rate their health on a scale from best (100) to worst (0).

9.4.13 Hospitalization Assessment

During study treatment and EFS and response follow-up periods (ie, through transformation to AML for HR MDS and CMML patients, through progression for low-blast AML patients, or until initiation of subsequent therapy for all patients, whichever occurs first), all hospitalizations since the previous assessment will be collected from all patients as indicated in the SOE (Appendix C). Examples of data to be collected are number and duration of inpatient hospitalizations, location of admission (eg, intensive care unit, hospital floor bed), and reason(s) for admission and primary diagnosis at discharge. Transfusion data will also be collected. For example, the number of patients who received packed RBCs and number of units received, number of patients who received a platelet transfusion and number of units received, and location of transfusion (inpatient vs outpatient).

9.4.14 Concomitant Medications and Procedures

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

9.4.15 AEs

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

9.4.16 Enrollment

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

Procedures for completion of the enrollment information are described in the IWRS and Study Manual(s).

9.4.17 ECGs

A 12-lead ECG will be administered at the time points specified in the SOE (Appendix C). Additional ECGs may be performed as clinically indicated.

9.4.18 Chest X-ray

A chest x-ray will be performed during Screening. If a chest x-ray or chest computed tomography scan was done within 2 months before randomization, the chest x-ray does not need to be done during Screening.

9.4.19 Clinical Laboratory Evaluations

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

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

- Samples are not able to be analyzed by central laboratory (for various reasons).
- Laboratory-dependent decisions needed for patient treatment have to be made before the availability of central lab results.

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

9.4.19.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the hematological and clinical chemistry parameters shown in Table 9.d, Table 9.e, and Table 9.f and urine samples for analysis of the parameters shown in Table 9.g will be obtained as specified in the SOE (Appendix C).

Table 9.d Hematology Tests

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

Coagulation testing (PT and aPTT) will be done at Screening and sent to the central laboratory.

Blood samples for analysis of reticulocyte counts and ferritin levels will be obtained as specified in the SOE (Appendix C) and sent to the central laboratory.

Table 9.e Complete Serum Chemistry Panel

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

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

Table 9.f Select Serum Chemistry Panel

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

Table 9.g Urinalysis with Microscopic Analysis

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

9.4.20 Disease Assessment

Formal disease assessments for study endpoints will be determined based on local bone marrow aspirate blast counts (blast counts from the bone biopsy may be used in the event the aspirate sample is inadequate and a biopsy was done), clinical laboratory evaluations performed at a central laboratory (local laboratory results may be used for time-sensitive clinical decisions), and local transfusion data. The investigator's assessment of disease will be entered into the eCRF for each time point.

Transformation to AML may occur in both MDS and CMML. In this study, transformation to AML is defined, according to WHO Classification [81] as a patient having ≥20% blasts in the blood or marrow AND increase of blast count by 50%. To illustrate:

- For patients with 5% to 9% blasts pretreatment: a ≥50% increase to >10% blasts constitutes progression of MDS.
- For patients with 10% to 19% blasts pretreatment: a ≥50% increase to >20% blasts constitutes transformation to AML.

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

Note that, according to the WHO Classification [81]:

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

As defined in Table 9.h and Table 9.i, additional assessment(s) of disease response for patients with MDS or CMML are based on the criteria outlined in the Modified IWG Response Criteria for MDS [2]; and additional assessments of disease response for patients with low-blast AML are based on the criteria outlined in the Revised Recommendations of the IWG for Diagnosis Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (Table 9.j).

Note that standard MDS guidelines [47] also recommend treatment for 6 cycles without altering dose or frequency of azacitidine regardless of cytopenias. Therefore, in this study, patients with HR MDS or CMML may be allowed to continue study treatment (either treatment arm), even if they meet the criteria for PD based only on bone marrow blast counts (without AML transformation), if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment.

Investigators should note that some AML patients may benefit from continued treatment even though their bone marrow blast counts may fluctuate over the course of the first 4 cycles. For example, 2 of the 6 responders in the single-agent pevonedistat study in relapsed/refractory AML had asymptomatic transient increases in bone marrow blasts after achieving a response. In these 2 cases, bone marrow blasts increased from less than 5% to more than 20%, and then decreased. In addition, another responder in that study had an asymptomatic transient increase in bone marrow blasts before achieving a response. In that case, bone marrow blasts almost doubled before response. These 3 patients were allowed to remain on study because their investigators felt they were clinically benefiting from continued treatment despite changes in their bone marrow blast counts. Therefore, patients with low-blast AML in this study may be allowed to continue study treatment (either treatment arm), even if they meet the criteria for PD based only on bone marrow blast counts, if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment. If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study.

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

Table 9.h Response Criteria for Altering Natural History of MDS and CMML

Category	Response Criteria
CR	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines (a) Persistent dysplasia will be noted (a) Peripheral blood (b) Hgb ≥11 g/dL Platelets ≥100×10^9/L Neutrophils ≥1.0×10^9/L Blasts 0%
PR	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥50% over pretreatment but still >5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment Peripheral blood: Any HI responses (see Table 9.i) will be noted separately, in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study.
Failure	Death during treatment or PD (as defined below), or progression to AML or a more advanced MDS or CMML FAB/WHO subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets **Note: Transient cytopenias during chemotherapy courses should not be considered relapse, as long as they recover to the previous levels.** Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality

Table 9.h Response Criteria for Altering Natural History of MDS and CMML

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

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

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

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

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

Table 9.i Response Criteria for HI for MDS and CMML

HI (a)	Response Criteria (Responses Must be At Least 8 Weeks in Duration)
Erythroid response (pretreatment, <11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.
Platelet response (pretreatment, $<100\times10^9$/L)	Absolute increase of $\geq30\times10^9$/L for patients starting with $>20\times10^9$/L platelets Increase from $<20\times10^9$/L to $>20\times10^9$/L and by at least 100%
Neutrophil response (pretreatment, $<1.0\times10^9$/L)	At least 100% increase and an absolute increase $>0.5\times10^9$/L
Progression or relapse after HI (b)	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥1.5 g/dL Transfusion dependence

To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb=hemoglobin, HI=hematologic improvement, RBC=red blood cell.
(a) Pretreatment counts will be the average of screening and Cycle 1 Day 1 predose samples.
(b) In the absence of another explanation, such as acute infection, a course of chemotherapy, gastrointestinal bleeding, hemolysis, and so forth. The 2 kinds of erythroid and platelet responses should be reported overall as well as by the individual response pattern.

The revised recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia will be used for assessment of disease response [3]. Investigators are encouraged to consult the reference for more detailed explanation of response criteria.

Table 9.j Response Criteria for AML

Category	Response Criteria
Morphologic Complete remission (CR)	A CR designation requires that the patient achieve the morphologic leukemia-free state and have an ANC of more than 1,000/µL and platelets of ≥100,000/µL. A morphologic leukemia-free state requires less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. Hemoglobin concentration or hematocrit has no bearing on remission status, although the patient must be independent of transfusions. There should be no residual evidence of extramedullary leukemia.
Morphologic complete remission with incomplete blood count recovery (CRi)	After chemotherapy, some patients fulfill all of the criteria for CR except for residual neutropenia (<1000/µL) or thrombocytopenia (<100,000/µL).
Cytogenetic CR	Reversion to a normal karyotype at CR or CRi
Partial remission (PR)	This designation requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. Thus, if the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pretreatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%. A repeat bone marrow aspiration after several weeks may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration. A value of ≤5% blasts may also be considered a PR if Auer rods are present.
Progressive disease (PD)	Because the IWG criteria for AML do not provide a standardized definition for PD, [3] in this protocol, PD is defined as one of the following: • >50% increase in bone marrow blasts from baseline value to >30% blasts. • >50% increase in circulating blasts from baseline value to >30% blasts in peripheral blood (in the exceptional case when bone marrow examination is not possible). • Development of biopsy-proven extramedullary disease, or new sites of extramedullary leukemia.
Relapse after CR	Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy). In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration.

AML= acute myelogenous leukemia, ANC= absolute neutrophil count, IWG= International Working Group.

9.4.21 Biomarker, Pharmacodynamic, and PK Samples

9.4.21.1 Primary Specimen Collection

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

Table 9.k Primary Specimen Collection

Specimen Name is Procedure in SOE (Appendix C) or Table A	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
Fresh bone marrow aspirate sample for cytogenetics	Fresh bone marrow	N/A	N/A	Central cytogenetic analysis in fresh bone marrow aspirate samples	Mandatory
Fresh bone marrow aspirate sample for cytogenetics at relapse	Fresh bone marrow	N/A	N/A	Central cytogenetic analysis in fresh bone marrow aspirate samples	Mandatory
Fresh bone marrow aspirate sample for molecular analysis	Fresh Bone Marrow	Frozen cell pellet	DNA	Molecular analysis in fresh bone marrow aspirate samples	Mandatory
			RNA		
		Frozen cell pellets	N/A		
Fresh bone marrow aspirate sample for molecular analysis at relapse	Fresh Bone Marrow	Frozen cell pellet	DNA	Molecular analysis in fresh bone marrow aspirate samples	Mandatory
			RNA		
		Frozen cell pellets	N/A		
Buccal epithelial cells sample for DNA	Buccal Swab	DNA	N/A	Biomarker measurements in buccal epithelial cells	Mandatory
Plasma samples for pevonedistat PK	Plasma	N/A	N/A	Pharmacokinetic measurements	Mandatory
Whole blood sample for molecular analysis	Blood	Frozen cell pellet	DNA	Molecular analysis in fresh blood samples	Mandatory
			RNA		
		Frozen cell pellets	N/A		
Whole blood sample for molecular analysis at relapse	Blood	Frozen cell pellet	DNA	Molecular analysis in fresh blood samples	Mandatory
			RNA		
		Frozen cell pellets	N/A		

9.4.22 PK Measurements

Blood samples (approximately 3 mL each) for the determination of pevonedistat (and its metabolites, if appropriate) plasma concentrations will be collected from all patients in the Combination Pevonedistat Plus Azacitidine Arm at the time points indicated in the SOE (Appendix C). The exact date and time of each sample collection, as well as the actual start and stop times of the study drug administration, should be recorded accurately, and particular care should be given to the recording of blood sampling times that occur close to the infusion.

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

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

9.4.23 Biomarker Measurements in Buccal Epithelial Cells

Buccal epithelial cell samples will be collected from patients in the Single-Agent Azacitidine Arm as well as patients in the Combination Pevonedistat Plus Azacitidine Arm as detailed in Table A). These samples (in addition to bone marrow aspirate and blood samples described in Section 9.4.24) will be used to identify biomarkers that are predictive of efficacy and/or safety of the combination of pevonedistat and azacitidine. Buccal epithelial cell samples will be used for the analysis of genotype variations in genes encoding DMEs or drug transporters that might be implicated in pevonedistat disposition. These samples may also be used in the interpretation of the tumor DNA sequencing data. This is a mandatory sample.

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

9.4.24 Bone Marrow Aspirate and Biopsy Collection and Analysis

Bone Marrow Sample Collection for Disease Assessment

Bone marrow aspirates and biopsies will be required during the study as detailed in Table A.

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

A bone marrow biopsy (in addition to bone marrow aspirate) is required only at Screening to confirm the diagnosis. However, a bone marrow biopsy may be collected with bone marrow aspirate in accordance with institutional guidelines. If a biopsy was done within 28 days before enrollment, this archival biopsy may be used and does not need to be repeated. Similarly if cytogenetic and mutation analysis was done within 28 days before enrollment, these results also may be used. A fresh bone marrow aspirate obtained at Screening or anytime before the first administration of study drug will be used for baseline molecular characterization. If a bone marrow biopsy is not collected routinely per country/institutional guidelines, it is not required.

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

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

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The bone marrow pathology reports, screening cytogenetics reports, and screening mutation analysis reports from the local laboratories will be submitted to the sponsor.

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

- Whenever a bone marrow *aspirate* is collected:
  - a peripheral blood smear will be sent to the central laboratory.
  - 2 to 3 unstained aspirate smears (either uncharged or charged slides) should be submitted to the central laboratory.
  - 1 aspirate smear from the local analysis should be submitted to the central laboratory.
- Whenever a bone marrow *biopsy* is collected, it should be submitted to the **central laboratory**.

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

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

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

- Bone marrow samples will also be sent to a central laboratory, in addition to those sent for local laboratory examination, for possible evaluation of blast count, if required. The procedure for handling, preparation and shipment of samples is outlined in the Laboratory Manual. Samples will be evaluated by the central laboratory at each time point (including any

unscheduled samples) and results will be reported to the sponsor. This evaluation will not be a real-time confirmation of progression, and results will not be routinely available to the clinical sites. Clinical decisions will be based on local laboratory blast count results. Discrepancies between local study site results and central laboratory results will be reviewed by the sponsor.

Following Cycle 4, bone marrow collection will be performed only as clinically indicated in patients who achieve CR. In all other patients who do not achieve CR, bone marrow assessments will be performed as described in Table A. Additional bone marrow aspirates may be performed if warranted by changes in peripheral blood counts.

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

Fresh Bone Marrow Aspirate Sample Collection for Molecular Analysis

Fresh bone marrow aspirate samples will be collected as described in Table A and will be sent to a specialty laboratory for molecular characterization to:

- Identify biomarkers that are predictive of efficacy and/or safety of the combination of pevonedistat and azacitidine: A portion of the bone marrow aspirate sample obtained at Screening will be sent to a specialty lab for baseline molecular characterization of the patient's MDS, CMML or low-blast AML.
- Evaluate changes in epigenetic patterns: Changes in epigenetic patterns (eg, methylation) following drug treatment will be determined by comparing epigenetic modifications in bone marrow aspirate samples obtained at Screening and after treatment (end of Cycle 2). Epigenetic changes might also be determined by evaluating changes in gene expression between bone marrow aspirate samples collected at Screening and after treatment.
- Determine depth and durability of response over time. Analysis will be done for disease burden following treatment using either flow cytometry, NGS, or proteomic based approaches.
- Evaluate mechanisms of treatment-emergent resistance: Bone marrow aspirates obtained at relapse will be evaluated for potential mechanisms of treatment-emergent resistance, such as somatic mutations in NAE subunits and key signaling pathways, or change in pathway activity.

Blood Sample Collection for Biomarker Analysis:

- Fresh blood samples will be collected as described in the SOE (Appendix C) and may be sent to a specialty laboratory for molecular characterization similar to that being proposed for the bone marrow aspirate sample.

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

9.5 Completion of Study Treatment (for Individual Patients)

A patient has completed the treatment if they discontinue treatment for any of the reasons listed in Section 9.7. Note that PD includes transformation to AML, relapse after CR for patients with low-blast AML, or other PD as defined in Section 9.4.20.

As detailed in Section 4.3, some patients in Study C15003 (single-agent pevonedistat in patients with relapsed/refractory AML) derived clinical benefit from continuing study treatment despite changes in their bone marrow blast counts. Standard MDS guidelines [47] also recommend treatment for 6 cycles without altering dose or frequency of azacitidine regardless of cytopenias. Therefore, in this study, patients may be allowed to continue study treatment (either treatment arm), even if they meet the criteria for PD based only on bone marrow blast counts (without AML transformation), if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor's project clinician (or designee). If a patient has <50% increase in blast count from pretreatment, then this is stable disease and the patient should remain on study. If a patient has ≥50% increase in blast count from pretreatment (without AML transformation), but is still deriving benefit, the patient may continue on study as agreed by the investigator and the sponsor's project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment.

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

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

- Patients with HR MDS or CMML at study enrollment who have not transformed to AML and have not started subsequent therapy following the EOT visit will enter EFS follow-up. If a patient with HR MDS or CMML at study enrollment subsequently transforms to AML (as defined in Section 9.4.20) the patient will then enter OS follow-up.
- Patients with low-blast AML at study enrollment who have not progressed and have not started subsequent therapy following the EOT visit will enter response follow-up. If a patient with low-blast AML subsequently progresses or relapses (as defined in Section 9.4.20) or initiates subsequent therapy during the response follow-up period, the patient will then enter OS follow-up period.
- Patients with HR MDS or CMML at study enrollment that has transformed to AML and patients with low-blast AML at study enrollment who have experienced PD or relapse after CR at the time of the EOT visit will enter OS follow-up immediately.

9.6 Completion of Study (for Individual Patients)

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

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- Study drug–related toxicity causing a study drug hold of >6 weeks (see Section 8.3.1).
- Unacceptable toxicity.
- Transformation to AML (in patients with HR MDS or CMML).
- PD.

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

- Disease relapse.

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

- AE.
- Protocol deviation.
- Subsequent anticancer therapy.
- Initiation of HSCT.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Appendix C). The primary reason for study drug discontinuation will be recorded on the eCRF. Further details should be recorded in the eCRF.

Patients who are randomized to a treatment arm but do not receive study drug for any reason will not be replaced.

9.8 Withdrawal of Patients From Study

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

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by subject.

- Death.
- Other.

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

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

9.9 Study Compliance

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

9.10 Posttreatment Follow-up Assessments (EFS Follow-up, Response Follow-up, and OS Follow-up)

Patients who discontinue study treatment will complete the EOT visit 30 days (+10) after the last dose of study drug. Patients will continue to be followed for EFS, Response, and OS endpoints as detailed in the SOE (Appendix C) and Table A. All subsequent therapies for MDS, CMML, and/or AML (as applicable) will be recorded, regardless if they are initiated before or after PD or transformation to AML.

Following the EOT visit, patients with HR MDS or CMML will enter EFS follow-up, if their disease has not transformed to AML. Patients will have monthly assessments to include physical exam, clinical blood tests, HRQOL assessments, hospitalization assessment, and disease assessment as outlined in the SOE (Appendix C). Patients who discontinue study treatment without evidence of progression (ie, PD or transformation to AML) will have a bone marrow aspirate and hematology tests (see Table 9.d) (all sent to the central laboratory) at the time of suspected progression. Patients who discontinue treatment while in CR or PR also will have a bone marrow aspirate and hematology tests (all sent to the central laboratory) at the time of suspected relapse (see SOE [Appendix C] and Table A). Patients will continue monthly EFS follow-up study visits until their disease transforms to AML (see Study Diagram in Appendix B). Patients who have started subsequent therapy will have EFS follow-up but will not be required to have monthly visits; at the time of suspected transformation to AML they will have a bone marrow aspirate and hematology tests (all sent to the central laboratory).

Following the EOT visit, patients with low-blast AML will enter response follow-up, if they have no evidence of disease progression and they have not started subsequent therapy. Patients will

have monthly assessments to include physical exam, clinical blood tests, HRQOL assessments, hospitalization assessment, and disease assessment as outlined in the SOE (Appendix C). Patients who discontinue study treatment while not in CR and without evidence of PD will have a bone marrow aspirate and hematology tests (all sent to central laboratory) at the time of suspected PD. Patients who discontinue treatment while in CR also will have a bone marrow aspirate and hematology tests (all sent to central laboratory) performed at the time of suspected relapse (see Table A). Patients will continue monthly response follow-up visits, until they relapse from CR or meet the criteria for PD (see Study Diagram in Appendix B).

Following the EFS and response follow-up visits, or the EOT visit (for patients with HR MDS or CMML who discontinue study treatment because of transformation to AML, or patients with low-blast AML who discontinue study treatment because of PD), patients will enter OS follow-up and will be contacted every 3 months until death to document subsequent therapies and survival status (see Study Diagram in Appendix B).

Note: Related SAEs must be reported to Takeda Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

9.11 Posttrial Access

9.11.1 Posttrial Access

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

9.11.2 Duration of PTA

If a PTA program should become an option for a patient, as described in Section 9.11.1, the sponsor may continue to provide pevonedistat to that patient through the PTA program. Continued access to pevonedistat for participants will be terminated for those individuals who no longer benefit from treatment (eg, their disease has progressed or treatment is no longer tolerable), the benefit-risk no longer favors the individual, an appropriate alternative therapy becomes available, or pevonedistat becomes available either commercially or via another access mechanism. PTA may be terminated in a country or geographic region where the development of pevonedistat has been suspended or stopped by the sponsor or where pevonedistat can no longer be supplied.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

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

10.1.2 AE Definition

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

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the

development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [4]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a WBC count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

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

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

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

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

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [4]The criteria are provided in the Study Manual.

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

10.3 Monitoring of AEs and Period of Observation

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

- AEs
  - Nonserious PTEs related to study screening procedures will be reported from the time of the signing of the ICF up to first dose of study drug and recorded in the eCRFs.
  - Treatment-emergent adverse events (TEAEs) will be reported from the first dose of any study drug through 30 days after administration of the last dose of any study drug and recorded in the eCRFs. TEAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).
- SAEs
  - Serious PTEs will be reported to the Takeda Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.
  - Related and unrelated treatment-emergent SAEs will be reported to the Takeda Department of Pharmacovigilance or designee from the first dose of study drug through the EOT visit, 30 (+10) days after administration of the last dose of study drug, and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

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

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

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

Call center	Phone number	E-mail	Fax
PPD			

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 Cognizant (refer to Section 10.2).

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

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

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Takeda Safety Monitoring

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

11.2 IRC

An IRC will be blinded to treatment arm and review all disease evaluation data from the study and determine disease status (response categories, transformation to AML, etc), according to the Modified IWG Response Criteria for MDS for patients with MDS or CMML and the Revised Recommendations of the IWG for Diagnosis Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia for patients with low-blast AML. Data from the IRC will not be provided to the investigator during the conduct of the study.

Details of the IRC will be captured in a charter.

11.3 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) supported by at least 1 independent statistician will review safety and efficacy data at the 2 planned interim analyses (IAs). The IDMC will review the outcomes at the first interim analysis (IA1) and the second interim analysis (IA2), and make recommendations on study conduct if needed. If the prespecified number of approximately 202 OS events for FA are expected (based on blinded study data) to be available close to the IA2, the IA2 (ie, EFS FA) and the FA (ie, OS FA) will be performed as a single analysis, when approximately 202 OS events and the adaptive EFS event size have occurred in patients with HR MDS. In this case, since the study will reach FA and the data will no longer be blinded after FA, an IDMC recommendation will not be necessary for this single analysis of IA2 and FA.

The adaptation decision rule used to re-estimate the number of EFS events for the EFS FA, will be prespecified and will be included in the IDMC charter only—not described in the protocol or statistical analysis plan (SAP). Therefore, the study team and the investigational site personnel will not have knowledge of the adaptation decision rule. (See Section 13.0 for more information on the statistical analyses.)

The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. If the study is terminated early based on the IDMC recommendation, the sponsor will notify the appropriate regulatory authorities. In addition, the IDMC will periodically review safety data at regularly scheduled meetings prespecified in the IDMC charter.

Study accrual will not be interrupted because of the scheduled safety reviews. The IDMC or pevonedistat study team may request an ad hoc meeting for any reason, including a significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, subject incidence rates of AEs (including all SAEs, treatment-related AEs, serious treatment-related events, and events requiring the discontinuation of study therapy) will be tabulated by system organ class (SOC), preferred term, and severity grade. Listings and/or narratives of on-study deaths and other serious and significant AEs, including any early withdrawals due to AEs, will be provided. Records of all meetings will be archived. The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to the sponsor. Further details will be provided in the IDMC charter.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

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

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

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties,

except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The following procedure is applied for the countries except for Japan. The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The following procedure is applied for Japanese sites only.

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and/or the head of the institution and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. The Kaplan-Meier (K-M) survival curves and 25th, 50th (median), and 75th percentiles (if estimable) will be provided along with their 95% CIs for time-to-event data.

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

Study Pevonedistat-3001 is a phase 3 study with 1 primary endpoint of EFS, 1 key secondary endpoint of OS, and adaptive event size re-estimation for EFS in patients with HR MDS [82]. There are 2 planned IAs and 1 FA. IA1 will evaluate futility for EFS and perform EFS event size re-estimation for patients with HR MDS for IA2. IA2 will be an EFS FA for patients with HR MDS (US submission) and the ITT population (ex-US submission). The FA will evaluate OS.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- **Safety population**: The safety population is defined as all patients who receive at least 1 dose of pevonedistat plus azacitidine or azacitidine alone. Patients will be analyzed according to the actual treatment they received. Patients who received any dose of pevonedistat will be included in the Combination Pevonedistat Plus Azacitidine Arm, and patients who did not receive any dose of pevonedistat and received at least 1 dose of azacitidine will be included in the Single-Agent Azacitidine Arm, regardless of their randomized treatment.
- **Intent-to-treat (ITT) population:** The ITT population is defined as all patients who are randomized. Patients in this population will be analyzed according to the treatment they were randomized to receive, regardless of any dosing errors.
- **Per-protocol (PP) population:** The PP population is a subgroup of the ITT population, consisting of all patients who receive at least 1 dose of study drug and do not have major protocol deviations, as determined by the study clinician. All decisions to exclude patients from the PP population will be made before the unblinding of the study.
- **Response-evaluable population:** The response-evaluable population is defined as patients who receive at least 1 dose of study drug, have a disease assessment at Screening (baseline evaluation), and at least 1 postbaseline disease assessment.

13.1.2 Analysis of Demographics and Other Baseline Disease Characteristics

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

13.1.3 Efficacy Analysis

All available efficacy data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. In general, missing data will be treated as missing, and no data imputation will be applied, unless otherwise specified.

All primary efficacy evaluations for the primary and key secondary efficacy endpoints will be conducted using patients with HR MDS, the ITT population, and other disease subpopulations (patients with low-blast AML, patients with HR MDS/CMML, and patients with HR CMML). In addition, sensitivity analysis may be performed using the PP population or response-evaluable population, when appropriate.

13.1.3.1 Analyses for Primary Efficacy Endpoint

EFS

The analysis of the primary endpoint, EFS, will use IRC assessment. The analysis of EFS for the US submission will be based on patients with HR MDS; the analysis for the ex-US submission will be based on the ITT population. For patients with HR MDS or CMML, an event is defined as death or transformation to AML, whichever occurs first; for patients with low-blast AML, an event is defined as death. EFS is defined as the time from randomization to the occurrence of an event. Detailed rules of handling missing assessments and censoring for the analysis of EFS will be described in the SAP. The Cui-Hung-Wang (CHW) [8] weighted log-rank test statistic will be used to maintain a strong control of type I error. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Sensitivity analyses for EFS will include:

- EFS assessed by investigator.
- EFS assessed by IRC in the PP population.

Subgroup analyses will be performed for EFS relative to baseline stratification factors and demographic data such as sex, race, and age, as appropriate. Details of the subgroups will be specified in the SAP.

13.1.3.2 Analyses of Key Secondary Efficacy Endpoint

The analysis of the key secondary endpoint, OS for the US submission will be based on patients with HR MDS; the analysis for the ex-US submission will be based on the ITT population. OS is

defined as the time from randomization to death from any cause. Patients without documentation of death at the time of the analysis will be censored at the date last known to be alive. The CHW test statistic will be used to compare the treatment and control groups with respect to OS. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect. The K-M survival curves and K-M medians (if estimable), along with their 95% CIs, will also be provided for each study group. Subgroup analyses for OS will be performed relative to baseline stratification factors and demographic data such as sex, race, and age, as appropriate. Details of the subgroups will be specified in the SAP. To adjust for the potential confounding effects of subsequent therapies after patients discontinue study therapy, additional sensitivity analyses for OS, such as marginal structural models (MSM) or inverse probability of censoring weight (IPCW) Cox models, may be conducted when appropriate.

13.1.3.3 Interim Analyses, Final Analysis, and Multiple Hierarchical Testing Procedure for Testing Primary and Key Secondary Efficacy Endpoints

There are 2 planned IAs and 1 FA. IA1 is planned to evaluate EFS for futility, and re-assess the EFS event size for patients with HR MDS for IA2. IA2 will be an FA of EFS in patients with HR MDS (for the US submission) and the ITT population (for the ex-US submission). The FA will evaluate OS.

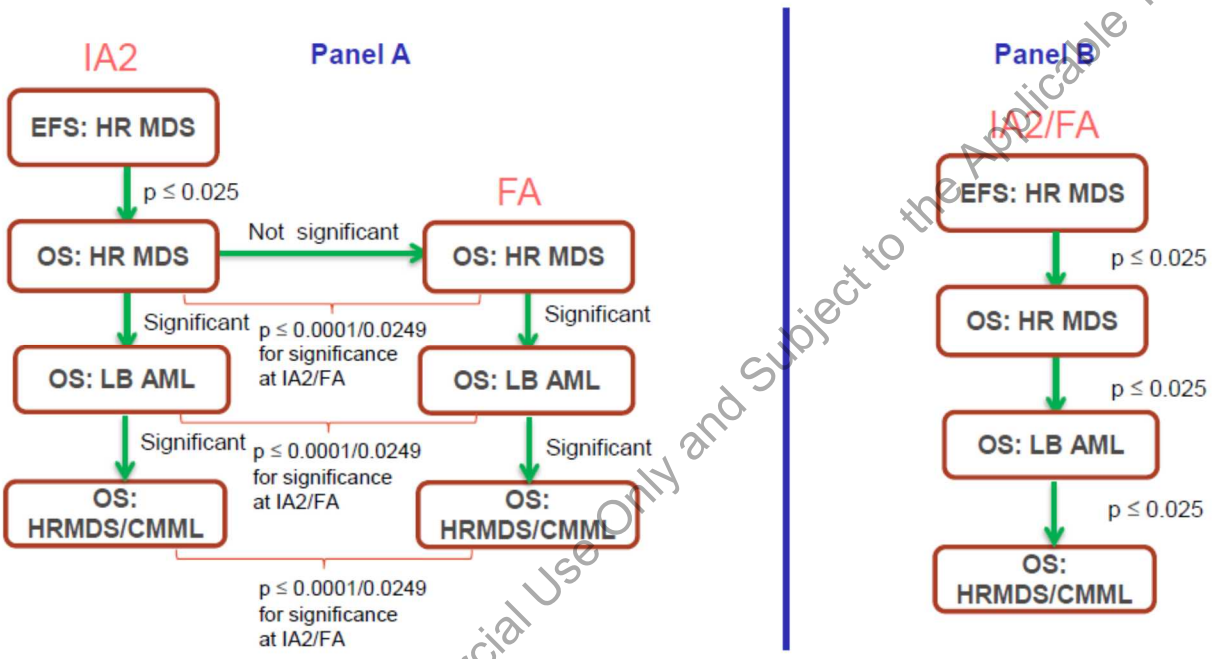
IA1 will be performed when approximately 74 EFS events have occurred in patients with HR MDS (around 50% information relative to the minimal planned event size of 147 EFS events for patients with HR MDS for the EFS FA at IA2). The study will stop if the EFS hazard ratio is >1.0 in all 3 of the following populations: patients with HR MDS, patients with HR MDS/CMML, and the ITT population. Otherwise, EFS event size re-estimation for patients with HR MDS will be performed using conditional power for the EFS FA that will be conducted at IA2.

IA2 (ie, EFS FA) will be performed when the approximate adaptive EFS event size (from a minimum of 147 to a maximum of 249), informed by the IDMC, has occurred in patients with HR MDS. The FA will be performed when approximately 202 OS events have occurred in patients with HR MDS. Separate multiple hierarchical testing procedures for the US submission and the ex-US submission will be adopted to test the primary endpoint of EFS and the key secondary endpoint of OS in the HR MDS population (US submission), the ITT population (ex-US submission), and other disease populations at IA2 and FA, with each procedure having a total 1-sided alpha of 0.025, as depicted on Panel A of Figure 13.a (US submission testing procedure) and on Panel A of Figure 13.b (ex-US submission testing procedure).

If the prespecified number of approximately 202 OS events for FA are expected (based on blinded study data) to be available close to the IA2, the IA2 (ie, EFS FA) and the FA (ie, OS FA) will be performed as a single analysis, when approximately 202 OS events and the adaptive EFS event size have occurred in patients with HR MDS. As originally planned, separate multiple hierarchical testing procedures for the US submission and the ex-US submission will be used to test the primary endpoint of EFS and the key secondary endpoint of OS in the HR MDS population (US submission), the ITT population (ex-US submission), and other disease populations at this single analysis, with a total 1-sided alpha of 0.025 for each procedure. The 2 hierarchical testing

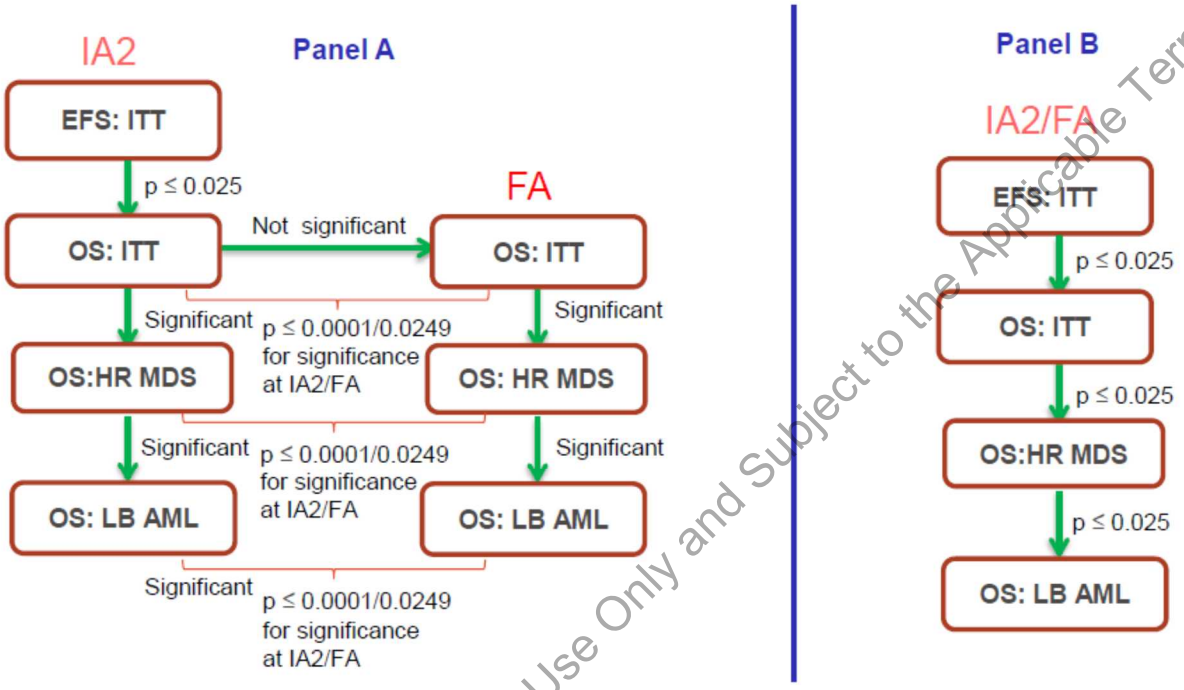
procedures originally specified at IA2 and FA will be performed as a single testing procedure, as depicted on Panel B of Figure 13.a (US submission testing procedure) and on Panel B of Figure 13.b (ex-US submission testing procedure).

Figure 13.a Multiple Hierarchical Testing Procedure at IA2 and FA for the US Submission



CMML=chronic myelomonocytic leukemia, EFS=event-free survival, FA=final analysis, HR MDS=higher-risk myelodysplastic syndromes, IA2=second interim analysis, IA2/FA=IA2 and FA are performed as a single analysis, LB AML=low-blast acute myelogenous leukemia, OS=overall survival, US=United States.

Figure 13.b Multiple Hierarchical Testing Procedure at IA2 and FA for the ex-US Submission



EFS=event-free survival, ex-US=all countries and regions excluding the United States, FA=final analysis, HR MDS=higher-risk myelodysplastic syndromes, IA2=second interim analysis, IA2/FA=IA2 and FA are performed as a single analysis, ITT=intent-to-treat, LB AML=low-blast acute myelogenous leukemia, OS=overall survival.

At IA2:

- For the US submission, EFS in patients with HR MDS will be tested first, only at IA2, at a 1-sided alpha of 0.025. The CHW weighted log-rank test statistics will be used. The weights are prespecified based on the observed number of EFS events in patients with HR MDS at IA1 and the minimum number of EFS events in patients with HR MDS planned for IA2.

  If the test of EFS in patients with HR MDS is statistically significant, OS in patients with HR MDS will be subsequently tested using the CHW weighted test statistic. If the test of OS in patients with HR MDS is statistically significant, then subsequent statistical testing using the CHW weighted test statistic will be performed in the following order: OS in patients with low-blast AML, and OS in patients with HR MDS/CMML.

- For the ex-US submission, EFS in the ITT population will be tested first, at a 1-sided alpha of 0.025. The CHW weighted test statistic will be used. The weights are prespecified based on the observed number of EFS events in patients with ITT at IA1 and the estimated number of EFS

events in the ITT population at IA2, which corresponds to the minimum number of EFS events in patients with HR MDS planned for IA2.

If the test of EFS in the ITT population is statistically significant, OS in the ITT population will be subsequently tested using the CHW weighted test statistic. If the test of OS in patients in the ITT population is statistically significant, then subsequent statistical testing using the CHW weighted test statistic will be performed, first for OS in patients with HR MDS and then for OS in patients with low-blast AML.

If EFS is not statistically significant in both patients with HR MDS and the ITT population at IA2, the study will stop for futility. If OS is statistically significant in both patients with HR MDS and the ITT population at IA2, the study will stop for efficacy. Otherwise, the study will continue to the FA.

At the FA:

- For the US submission, if the test of OS in the HR MDS population fails to achieve statistical significance at IA2, OS in patients with HR MDS will be tested first using the CHW weighted test statistic. If statistical significance is achieved, subsequent statistical testing will be performed in the following order: OS in patients with low-blast AML, and OS in patients with HR MDS/CMML. The CHW weighted test statistic will be used for both tests.
- For the ex-US submission, if the test of OS in the ITT population fails to achieve statistical significance at IA2, OS in the ITT population will be tested first using the CHW weighted test statistic. If statistical significance is achieved, subsequent statistical testing will be performed, first for OS in patients with HR MDS and then for OS in patients with low-blast AML. The CHW weighted test statistic will be used for both tests.

EFS in the HR MDS population (US submission) and in the ITT population (ex-US submission) will be tested first, only at IA2 using the 1-sided alpha of 0.025. All other tests specified in the multiple hierarchical testing procedures (Figure 13.a [US submission] and Figure 13.b [ex-US submission]) that will be performed at IA2 and FA, including OS in the HR MDS population (US submission), OS in the ITT population (ex-US submission), OS in the low-blast AML population, and OS in the HR MDS/CMML population, will use a 1-sided alpha of 0.0001 at IA2 and the remaining 1-sided alpha of 0.0249 at FA. The testing procedures for the US and ex-US submissions will be performed independently. Under the sequential procedure, the testing will be stopped once 1 test fails to achieve statistical significance. Naturally, no benefit will be claimed for untested hypotheses.

When the EFS event size for the HR MDS population for IA2 is re-estimated at IA1, the numbers of OS and EFS events in other populations of interest for IA2 will be changed accordingly. The use of CHW weighted test statistics [8] can preserve a type-I error rate when the event sizes are changed. In addition, the multiple testing procedures (multiple hypotheses and multiple looks) that apply the sequential procedures, and the specified alpha spending approach, also maintain control of the familywise type I error rate, as discussed in Glimm et al [9].

The analyses will also be performed for EFS in the HR CMML population at IA2 and for OS in the HR CMML population at IA2 and FA. They will not be included in the above multiple testing procedures and are for exploratory purposes only.

13.1.3.4 Analyses of Other Secondary Efficacy Endpoints

Other secondary efficacy parameters are: 6-month and 1-year survival rates; time to AML transformation; rate of CR (includes CR in patients with HR MDS or CMML, or low-blast AML), CR+CRi in patients with low-blast AML, CR+marrow CR in patients with HR MDS or CMML, CR+PR+HI in patients with HR MDS or CMML, CR+marrow CR+PR in patients with HR MDS or CMML, CR+marrow CR+PR+HI in patients with HR MDS or CMML, overall response, overall response by Cycle 6, and overall response 2; duration of CR, CR+CRi, overall response, and overall response 2; RBC and/or platelet transfusion independence; duration of RBC and/or platelet transfusion independence; time to first CR or PR or CRi; percent of patients who have at least 1 inpatient hospital admission(s) related to HR MDS or CMML, or low-blast AML; time to PD, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death; and ORR, EFS and OS in patients that have *TP53* mutations, 17p deletions, and/or are determined to be in an adverse cytogenetic risk group in both treatment arms.

Disease response-related endpoints will be analyzed using IRC assessments.

6-month and 1-year Survival Rates

K-M estimates and the 95% CIs of 6-month and 1-year survival rates will be provided based on patients with HR MDS, the ITT population, and other disease subpopulations (patients with low-blast AML, patients with HR MDS/CMML, and patients with HR CMML) separately.

Time to AML Transformation

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

Rate of CR (CR in patients with HR MDS or CMML, or low-blast AML), CR+CRi in patients with low-blast AML, CR+marrow CR (in patients with HR MDS or CMML), CR+PR+HI (in patients with HR MDS or CMML), CR+marrow CR+PR (in patients with HR MDS or CMML), CR+marrow CR+PR+HI (in patients with HR MDS or CMML), overall response (CR+PR in patients with HR MDS or CMML; CR+CRi+PR in patients with low-blast AML), overall response by Cycle 6 ([CR+PR in patients with HR MDS or CMML; CR+CRi+PR in patients with low-blast AML] by Cycle 6), and overall response 2 (CR+PR+HI in patients with HR MDS or CMML; CR+CRi+PR in patients with low-blast AML)

Rate of CR (CR in patients with HR MDS or CMML, or low-blast AML), CR+CRi in patients with low-blast AML, CR+marrow CR (in patients with HR MDS or CMML), CR+PR+HI (in patients with HR MDS or CMML), CR+marrow CR+PR (in patients with HR MDS or CMML), CR+ marrow CR + PR + HI (in patients with HR MDS or CMML), overall response (CR+PR in patients with HR MDS or CMML; CR+CRi+PR in patients with low-blast AML), overall response by Cycle 6 ([CR+PR in patients with HR MDS or CMML; CR+CRi+PR in patient with low-blast AML] by Cycle 6), and overall response 2 (CR+PR+HI in patients with HR MDS or CMML; CR+CRi+PR in patients with low-blast AML) are disease response-related endpoints, which will be analyzed using IRC assessments for the Response-Evaluable population. Stratified CMH test will be used to compare the 2 treatment arms. The difference in rates and the associated 95% CIs will be presented.

Duration of CR, CR+CRi (in patients with low-blast AML), Overall Response, and Overall Response 2

Duration of CR, CR+CRi (in patients with low-blast AML), overall response, and overall response 2 will be summarized descriptively using the K-M method.

Rate of RBCs and/or Platelet Transfusion Independence

Analysis of RBC and/or platelet transfusion independence will be based on patients with HR MDS, the ITT population, and other disease subpopulations (patients with low-blast AML, patients with HR MDS/CMML, and patients with HR CMML), separately.

A patient is defined as RBC and/or platelet-transfusion independent if he/she receives no RBC and/or platelet transfusions for a period of at least 8 weeks [16,45] during the time period from the first dose of study drug administration through 30 days after the last dose of any study drug. Rate of RBC and/or platelet-transfusion independence is defined as number of patients who become RBC and/or platelet transfusion independent divided by the number of patients who are RBC and/or platelet transfusion dependent at Baseline. Rate of RBC and/or platelet transfusion independence, will be summarized by treatment group. Stratified CMH test will be used to compare the 2 treatment arms. The difference in rates and the associated 95% CIs will be presented.

Duration of RBC and/or Platelet Transfusion Independence

Analysis of duration of RBC and/or platelet transfusion independence will be based on patients with HR MDS, the ITT population, and other disease subpopulations (patients with low-blast

AML, patients with HR MDS/CMML, and patients with HR CMML) who are RBC and/or platelet transfusion independent during the trial, separately.

Duration of transfusion independence is defined as the longest time between the last RBC and/or platelet transfusion before the start of the RBC and/or platelet transfusion-independent period and the first RBC and/or platelet transfusion after the start of the transfusion-independent period, which occurs ≥8 weeks later.

Time to First CR or PR or CRi (in patients with low-blast AML)

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

Time to first CR or PR or CRi is defined as time from randomization to first documented CR or PR or CRi, whichever occurs first. Time to first CR or PR or CRi will be analyzed similarly to time to AML transformation.

Rates of HI

Rates of HI will be analyzed using IRC assessments for the Response-Evaluable population of patients with HR MDS, patients with HR MDS/CMML, and patients with HR CMML. Stratified CMH test will be used to compare the 2 treatment arms. The difference in rates and the associated 95% CIs will be presented.

Percent of Patients Who Have at Least One Inpatient Hospital Admission Related to HR MDS or CMML, or AML

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

The number and percentage of patients who have at least one inpatient hospital admission(s) related to HR MDS or CMML or AML will be summarized by treatment group. The rate difference and the associated 95% CIs will be provided.

Time To PD, Relapse after CR (low-blast AML), Relapse after CR or PR (HR MDS/CMML), or Death

Analysis of time to PD, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death will be based on the ITT population and the disease subpopulations (patients with HR MDS/CMML, patients with HR MDS, patients with HR CMML, and patients with low-blast AML), separately.

Time to PD, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death is defined as the time from the date of randomization until the date of the first documentation

of disease progression, relapse after CR (low-blast AML), relapse after CR or PR (HR MDS/CMML), or death due to any cause, whichever occurs first. Time to PD, relapse after CR or PR, or death will be analyzed similarly as time to AML transformation.

ORR, EFS, and OS in Patients who Have *TP53* Mutations, 17p deletions, and/or are Determined to be in Adverse Cytogenetic Risk Group

ORR, EFS, and OS in patients who have *TP53* mutations and/or 17p deletions, and are determined to be in an adverse cytogenetic risk group will be analyzed using the similar method as ORR, EFS, and OS in patients with HR MDS, the ITT population, and other disease subpopulations (patients with low-blast AML, patients with HR MDS/CMML, and patients with HR CMML) separately.

13.1.4 PK Analysis

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

The PK data collected in this study are intended to contribute to future population PK analyses of pevonedistat. These analyses may additionally include data collected in other pevonedistat clinical studies. The analysis plan for population PK analysis will be defined separately and results of these analyses will be reported separately.

13.1.5 PRO Analyses

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

13.1.6 Safety Analysis

All available safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

Safety population will be used for all safety analyses.

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

TEAEs are AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of any study drug. AEs will be tabulated according to the MedDRA by SOC, high-level term, and preferred term, and will include the following categories:

- TEAEs.

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

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

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

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

Baseline and change from baseline ECOG PS will be summarized.

All concomitant medications collected from Screening through the study period will be classified to preferred terms according to the WHO Drug Dictionary. All blood (RBC, platelet) transfusions will also be reviewed to determine transfusion dependence or independence, as detailed in Section 9.4.14.

Thirty-/60-day mortality rate is defined as the proportion of patients who survive at most 30/60 days from the first dose of study drug, which will be summarized by treatment arm based on the Safety population.

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

13.1.7 EFS Events Re-estimation at IA1

The EFS event-size adaptation rule is a prespecified stepwise function to avoid the back calculation problem resulting from 1 event size corresponding to either barely promising or highly promising interim results. The event-size adaptation rule will be designed by the sponsor's independent design statistician and approved by the sponsor's head of biostatistics. Neither the independent design statistician nor the sponsor's head of biostatistics are involved in the study conduct.

The adaptation rules will be outlined in a separate document and will not be accessible to the sponsor's study team until completion of the study. The rules will be available only to the

sponsor's independent design statistician, the sponsor's head of biostatistics, the IDMC, and the statistics representative in the sponsor's executive committee (if different from the sponsor's head of biostatistics).

The conditional power for EFS will be calculated based on patients with HR MDS at IA1 to re-estimate the number of EFS events for patients with HR MDS for the EFS FA if EFS hazard ratio ≤1.0 in patients with HR MDS, in patients with HR MDS/CMML, or in the ITT population. The prespecified EFS event size re-estimation adaptation rule is a step function, which is calculated on the basis of Liu and Hu [82].

To ensure integrity in this open-label study, it will be designed with the following features:

- The adaptation decision rule will be prespecified before the study starts and will be included in the IDMC charter appendix only—not described in the protocol or SAP. It will be accessed only by IDMC, head of biostatistics and sponsor design statistician, who are not involved in the study conduct. Therefore, the study team and the investigational site personnel will not have knowledge of the adaptation decision rule.
- The IDMC will determine EFS event size in patients with HR MDS for IA2 at IA1. An IDMC charter will be developed to include details regarding all statistical evaluations and operational procedures for the IAs and EFS event size adaptation.
- The EFS event size adaptation rule will be chosen such that the interim results cannot be derived from the increase in EFS events.
- A separate statistical reporting organization will be selected to facilitate the activities of the IDMC. This organization will be responsible for handling the unblinded data and producing materials needed for the IDMC.
- Sponsor employees and clinical research organization employees working on the conduct of this study will be blinded throughout the study to analysis results that are not publicly released and to the adaptation rule.
- Investigators from all investigational sites will not have access to any analysis results that are not publicly released or to the adaptation rule during study conduct.

13.2 Determination of Sample Size

There is 1 primary endpoint, of EFS, and 1 key secondary endpoint of OS. The total number of patients was calculated on the basis of maintaining 83% power to test the key secondary endpoint OS in patients with HR MDS at a 1-sided alpha level of 0.025, as well as sufficient representation of patients with low-blast AML. The study is also adequately powered to test the primary endpoint, EFS, in patients with HR MDS and in the ITT population for full approval in the US submission and the ex-US submission, respectively, as well as to test OS in the ITT population.

A total of approximately 450 patients, including at least 350 patients with HR MDS or CMML and at least 100 patients with low-blast AML, will be enrolled, with 320 patients with HR MDS required to obtain 202 OS events in patients with HR MDS. Patients will be randomized in a

1:1 ratio to the 2 treatment arms, stratified by low-blast AML, IPSS-R risk group of very high, high, or intermediate for MDS/CMML [1]. Assuming an enrollment rate that increases from an initial 1 patient per month to 22 patients per month after the first 10 months, with a dropout rate of approximately 10%, the study will take approximately 27 months for patient accrual and an additional approximately 38 months for follow-up from the enrollment of the last patient.

The minimal planned event size of 147 EFS events from patients with HR MDS is based on an optimistic assumption of a hazard ratio of 0.585 (median EFS of 17.09 months in the combination arm versus 10 months in the azacitidine alone arm) with approximately 90% power at a 1-sided alpha of 0.025. The maximal planned event size of 249 EFS events from patients with HR MDS is based on a relatively conservative assumption of a hazard ratio of 0.663 (median EFS of 15.08 months in the combination arm versus 10 months in the azacitidine alone arm) with approximately 90% power at a 1-sided alpha of 0.025. It is projected that the EFS event size from the ITT population ranges approximately from 158 (approximately 92% power, 1-sided alpha=0.025, hazard ratio=0.585, median EFS of 22.22 months in the combination arm versus 13 months in the azacitidine alone arm) to 305 (approximately 95% power, 1-sided alpha=0.025, hazard ratio=0.663, median EFS of 19.61 months in the combination arm versus 13 months in the azacitidine alone arm).

With the assumption of a hazard ratio of 0.663 for OS in patients in HR MDS (median OS of 36.95 months in the combination arm versus 24.5 months in the azacitidine alone arm), 202 OS events provide approximately 83% power at a 1-sided alpha of 0.025. It is projected that approximately 280 OS events will occur to the ITT population, providing approximately 93% power to test OS in the ITT population (1-sided alpha=0.025, hazard ratio=0.663, median OS of 36.95 months in the combination arm versus 24.5 months in the azacitidine alone arm).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches

should be used only where allowed by the local Health Authority, privacy laws, and permitted by the IRB/IEC.

14.2 Protocol Deviations

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

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

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

The procedure below applies to Japanese sites only.

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the

revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

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

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

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, applicable laws and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

1. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65.
2. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108(2):419-25.
3. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21(24):4642-9.
4. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.
5. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndromes. British Journal of Haematology 1982;51(2):189-99.
6. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114(5):937-51.
7. Walter R, Othus M, Borthakur G, Ravandi F, Cortes J, Pierce S, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. J Clin Oncol 2011;29:4417-23.
8. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics 1999;55(3):853-7.
9. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Statistics in Medicine 2010;29(2):219-28.
10. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391-405.
11. Sekeres MA, Gerds AT. Established and novel agents for myelodysplastic syndromes. ASH Education Program Book 2014;2014(1):82-9.
12. Zeidan AM, Linhares Y, Gore SD. Current therapy of myelodysplastic syndromes. Blood Reviews 2013;27(5):243-59.
13. Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. Journal of Clinical Oncology 2014;32(24):2541-52.
14. Sekeres MA, Cutler C. How we treat higher-risk myelodysplastic syndromes. Blood 2014;123(6):829-36.

15. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. New England Journal of Medicine 2006;355(14):1456-65.
16. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncology 2009;10(3):223-32.
17. Kantarjian H, O'Brien S, Cortes J, Wierda W, Faderl S, Garcia-Manero G, et al. Therapeutic advances in leukemia and myelodysplastic syndrome over the past 40 years. Cancer 2008;113(7 Suppl):1933-52.
18. Mufti GJ, Potter V. Myelodysplastic syndromes: who and when in the course of disease to transplant. Hematology 2012;2012:49-55.
19. Luger SM, Ringden O, Zhang MJ, Perez WS, Bishop MR, Bornhauser M, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. Bone Marrow Transplant 2012;47(2):203-11.
20. Sekeres MA, Schoonen WM, Kantarjian H, List A, Fryzek J, Paquette R, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. Journal of the National Cancer Institute 2008;100(21):1542-51.
21. Sekeres MA, Tiu RV, Komrokji R, Lancet J, Advani AS, Afable M, et al. Phase 2 study of the lenalidomide and azacitidine combination in patients with higher-risk myelodysplastic syndromes. Blood 2012;120(25):4945-51.
22. Prebet T, Sun Z, Figueroa ME, Ketterling R, Melnick A, Greenberg PL, et al. Prolonged administration of azacitidine with or without entinostat for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: results of the US Leukemia Intergroup trial E1905. Journal of Clinical Oncology 2014;32(12):1242-8.
23. Zandberg DP, Huang TY, Ke X, Baer MR, Gore SD, Smith SW, et al. Treatment and outcomes for chronic myelomonocytic leukemia compared to myelodysplastic syndromes in older adults. Haematologica 2013;98(4):584-90.
24. Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th Edition, Vol. 2. Lyon: IARC Press; 2008.
25. Emanuel PD. Mixed myeloproliferative and myelodysplastic disorders. Current Hematologic Malignancy Reports 2007;2(1):9-12.
26. Ades L, Sekeres MA, Wolfromm A, Teichman ML, Tiu RV, Itzykson R, et al. Predictive factors of response and survival among chronic myelomonocytic leukemia patients treated with azacitidine. Leukemia Research 2013;37(6):609-13.
27. Germing U, Kundgen A, Gattermann N. Risk assessment in chronic myelomonocytic leukemia (CMML). Leukemia & Lymphoma 2004;45(7):1311-8.

28. Onida F, Kantarjian HM, Smith TL, Ball G, Keating MJ, Estey EH, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. Blood 2002;99(3):840-9.
29. Parikh SA, Tefferi A. Chronic myelomonocytic leukemia: 2012 update on diagnosis, risk stratification, and management. American Journal of Hematology 2012;87(6):610-9.
30. Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Della Porta MG, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood 2013;121(15):3005-15.
31. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. Journal of Clinical Oncology 2002;20(10):2429-40.
32. Shih AH, Levine RL. Molecular biology of myelodysplastic syndromes. Seminars in Oncology 2011;38(5):613-20.
33. Thol F, Kolking B, Damm F, Reinhardt K, Klusmann JH, Reinhardt D, et al. Next-generation sequencing for minimal residual disease monitoring in acute myeloid leukemia patients with FLT3-ITD or NPM1 mutations. Genes, Chromosomes & Cancer 2012;51(7):689-95.
34. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. New England Journal of Medicine 2016;374(23):2209-21.
35. Soucy TA, Smith PG, Milhollen MA, Berger AJ, Gavin JM, Adhikari S, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. Nature 2009;458:732-6.
36. Lin JJ, Milhollen MA, Smith PG, Narayanan U, Dutta A. NEDD8-targeting drug MLN4924 elicits DNA rereplication by stabilizing Cdt1 in S phase, triggering checkpoint activation, apoptosis, and senescence in cancer cells. Cancer Res 2010;70(24):10310-20.
37. Milhollen MA, Narayanan U, Soucy TA, Veiby PO, Smith PG, Amidon B. Inhibition of NEDD8-activating enzyme induces rereplication and apoptosis in human tumor cells consistent with deregulating CDT1 turnover. Cancer Res 2011;71(8):3042-51.
38. Swords RT, Coutre S, Maris MB, Zeidner JF, Foran JM, Cruz J, et al. Pevonedistat, a first-in-class NEDD8-activating enzyme (NAE) inhibitor, combined with azacitidine, in patients with AML. Blood 2018;131(13):1415-24.
39. Swords RT, Savona MR, Maris MB, Erba HP, Berdeja JG, Foran JM, et al. Pevonedistat (MLN4924), an investigational, first-in-class NAE inhibitor, in combination with azacitidine in elderly patients with acute myeloid leukemia (AML) considered unfit for conventional chemotherapy: Updated results from the phase 1 C15009 trial. 2014 Annual Meeting of the American Society of Hematology (ASH); 06-09 December 2014; San Francisco, CA.
40. Swords RT, Erba HP, DeAngelo DJ, Bixby DL, Altman JK, Maris M, et al. Pevonedistat (MLN4924), a First-in-Class NEDD8-activating enzyme inhibitor, in patients with acute

myeloid leukaemia and myelodysplastic syndromes: a phase 1 study. Br J Haematol 2015;169(4):534-43.

41. Swords R, Coutre S, Maris M, Zeidner J, Foran J, Cruz J, et al. Results of a Clinical Study of Pevonedistat (Pev), a First-in-Class NEDD8-Activating Enzyme (NAE) Inhibitor, Combined with Azacitidine (Aza) in Older Patients (Pts) with Acute Myeloid Leukemia (AML). ASH 58th Annual Meeting & Exposition, American Society of Hematology; December 3-6, 2016; San Diego, CA, USA. 98.
42. Swords R, Erba H, DeAngelo D, Smith P, Pickard M, Dezube B, et al. The Novel, Investigational NEDD8-Activating Enzyme Inhibitor MLN4924 In Adult Patients with Acute Myeloid Leukemia (AML) or High-Grade Myelodysplastic Syndromes (MDS): A Phase 1 Study. Blood (ASH Annual Meeting Abstracts) 2010;116(21):abstr 658.
43. Garcia-Delgado R, de Miguel D, Bailen A, Gonzalez JR, Bargay J, Falantes JF, et al. Effectiveness and safety of different azacitidine dosage regimens in patients with myelodysplastic syndromes or acute myeloid leukemia. Leukemia Research 2014;38(7):744-50.
44. VIDAZA (azacitidine for injection) for SC or IV use [package insert]. Summit, NJ: Celgene Corporation, 2014.
45. Silverman LR, McKenzie DR, Peterson BL, Holland JF, Backstrom JT, Beach CL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. Journal of Clinical Oncology 2006;24(24):3895-903.
46. Grinblatt DL, Sekeres MA, Komrokji RS, Swern AS, Sullivan KA, Narang M. Patients with myelodysplastic syndromes treated with azacitidine in clinical practice: the AVIDA registry. Leukemia & Lymphoma 2015;56(4):887-95.
47. NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes version 2. National Comprehensive Cancer Network. 2017.
48. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424-47.
49. Metzeler KH, Becker H, Maharry K, Radmacher MD, Kohlschmidt J, Mrozek K, et al. ASXL1 mutations identify a high-risk subgroup of older patients with primary cytogenetically normal AML within the ELN Favorable genetic category. Blood 2011;118(26):6920-9.
50. Metzeler KH, Maharry K, Radmacher MD, Mrozek K, Margeson D, Becker H, et al. TET2 mutations improve the new European LeukemiaNet risk classification of acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 2011;29(10):1373-81.
51. Patel JP, Gonen M, Figueroa ME, Fernandez H, Sun Z, Racevskis J, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med 2012;366(12):1079-89.

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

53. Papaemmanuil E, Cazzola M, Boultwood J, Malcovati L, Vyas P, Bowen D, et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. New England Journal of Medicine 2011;365(15):1384-95.

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

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

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

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

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

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

60. Takahashi K, Patel K, Bueso-Ramos C, Zhang J, Gumbs C, Jabbour E, et al. Clinical implications of TP53 mutations in myelodysplastic syndromes treated with hypomethylating agents. Oncotarget 2016;7(12):14172-87.

61. Rucker FG, Schlenk RF, Bullinger L, Kayser S, Teleanu V, Kett H, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood 2012;119(9):2114-21.

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

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

64. Ivey A, Hills RK, Simpson MA, Jovanovic JV, Gilkes A, Grech A, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. New England Journal of Medicine 2016;374(5):422-33.

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

66. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. New England Journal of Medicine 2016;375(21):2023-36.

67. Braulke F, Jung K, Schanz J, Gotze K, Muller-Thomas C, Platzbecker U, et al. Molecular cytogenetic monitoring from CD34+ peripheral blood cells in myelodysplastic syndromes: first results from a prospective multicenter German diagnostic study. Leukemia Research 2013;37(8):900-6.

68. Martin R, Palomo L, Ganster C, Acha P, Dierks S, Mallo M, et al. In MDS targeted deep sequencing of CD34+ blood cells but not peripheral blood mononuclear cells give results which are representative for bone marrow. ASH 2016. 94431.

69. Basch E, Geoghegan C, Coons SJ, Gnanasakthy A, Slagle AF, Papadopoulos EJ, et al. Patient-Reported Outcomes in Cancer Drug Development and US Regulatory Review: Perspectives From Industry, the Food and Drug Administration, and the Patient. JAMA Oncology 2015;1(3):375-9.

70. Acquadro C, Regnault A. Patient-reported outcomes in drug development for hematology. Hematology 2015;2015:496-500.

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

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

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

74. Basch E, Abernethy AP, Mullins CD, Reeve BB, Smith ML, Coons SJ, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. Journal of Clinical Oncology 2012;30(34):4249-55.

75. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research 2011;20(10):1727-36.

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

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

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

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

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

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

82. Liu Y, Hu M. Testing multiple primary endpoints in clinical trials with sample size adaptation. Pharmaceutical Statistics 2016;15(1):37-45.

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

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

Appendix A Treatment-Related Mortality Rates

Table 4. TRM Rates According to TRM Score and Age Using Basic Three-Component Prediction Model

	SWOG Patients (years of age)*				MDA Patients (years of age)			
	> 60		≤ 60		> 60		≤ 60	
TRM Score	No.	%	No.	%	No.	%	No.	%
0-3†	7 of 68	10	25 of 558	4	2 of 96	2	28 of 879	3
4-6‡	27 of 218	12	11 of 88	13	63 of 650	10	44 of 223	20
≥ 7§	35 of 113	31	0	0	84 of 390	22	0	0

NOTE. Calculation of score: 0 × (age < 61 years) + 2 × (age 61 to 70 years) + 4 × (age ≥ 71 years) + 0 × (PS = 0) + 2 × (PS = 1) + 4 × (PS > 1) + 0 × (platelets < 50) + 1 × (platelets ≥ 50).

Abbreviations: MDA, MD Anderson Cancer Center; PS, performance status; SWOG, Southwest Oncology Group; TRM, treatment-related mortality.

*Inclusion of only 1,045 SWOG patients in Table (rather than entire SWOG cohort of 1,127 patients, as in Appendix Table A1, online only) reflects 82 patients with missing values for platelet counts. TRM rates were 10% for subset of 1,045 patients and 11% for entire SWOG cohort.

†Low risk: score 0-3. Age 61 to 70 years with PS = 0; age ≤ 60 years with PS ≤ 1.

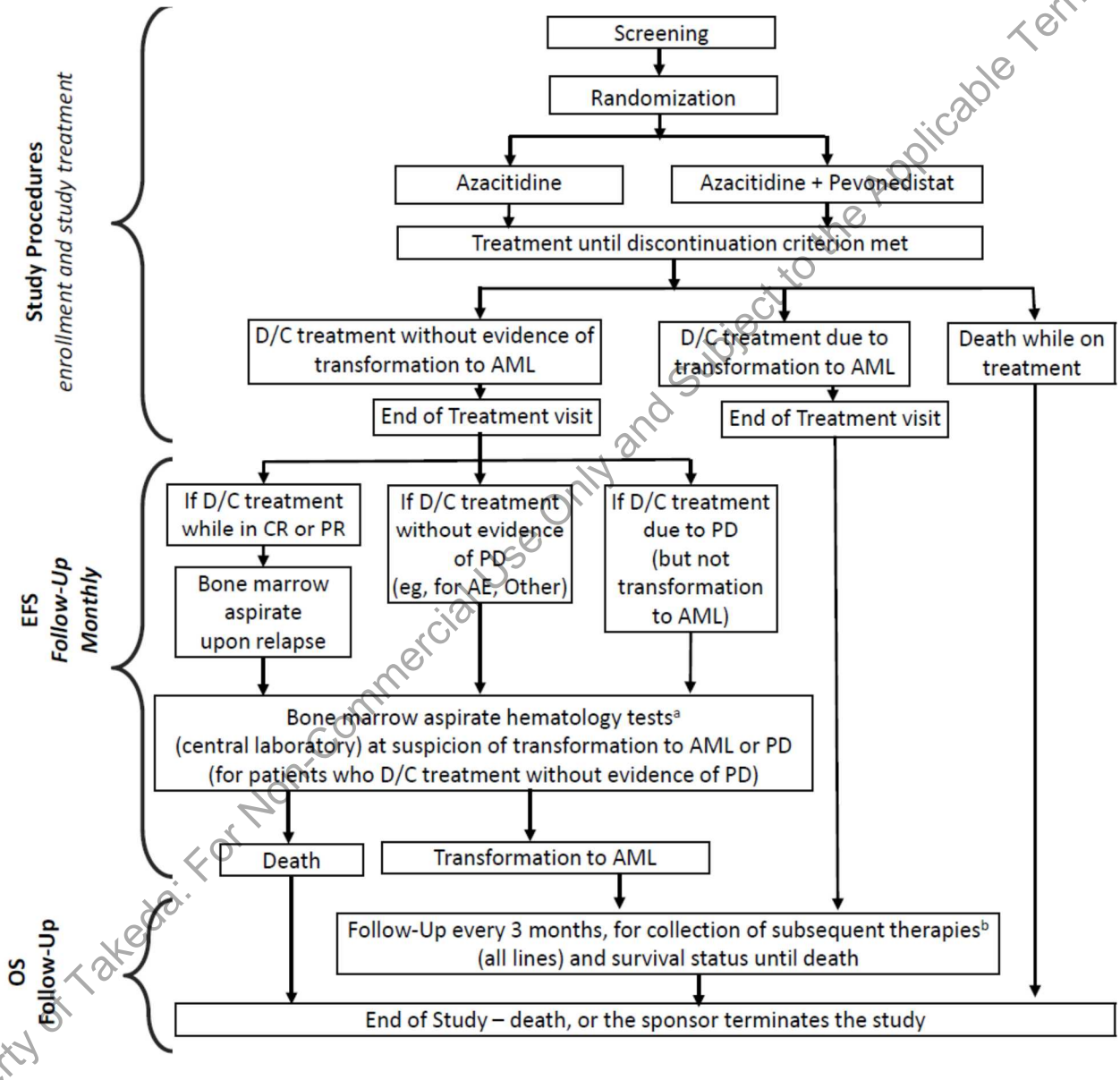
‡Intermediate risk: score 4-6. Age ≥ 71 years with PS = 0, platelets < 50; age 61 to 70 years with PS = 1; age 61 to 70 years with PS > 1 and platelets < 50; age ≤ 60 years with PS > 1.

§High risk: score ≥ 7. Age ≥ 71 years with PS = 1 and platelets ≥ 50; age ≥ 71 years with PS > 1; age 61 to 70 years with PS > 1 and platelets ≥ 50.

Source: Walter et al 2011[7].

Appendix B Study Diagrams

STUDY OVERVIEW DIAGRAM 1:
PATIENTS WITH HR MDS OR CMML



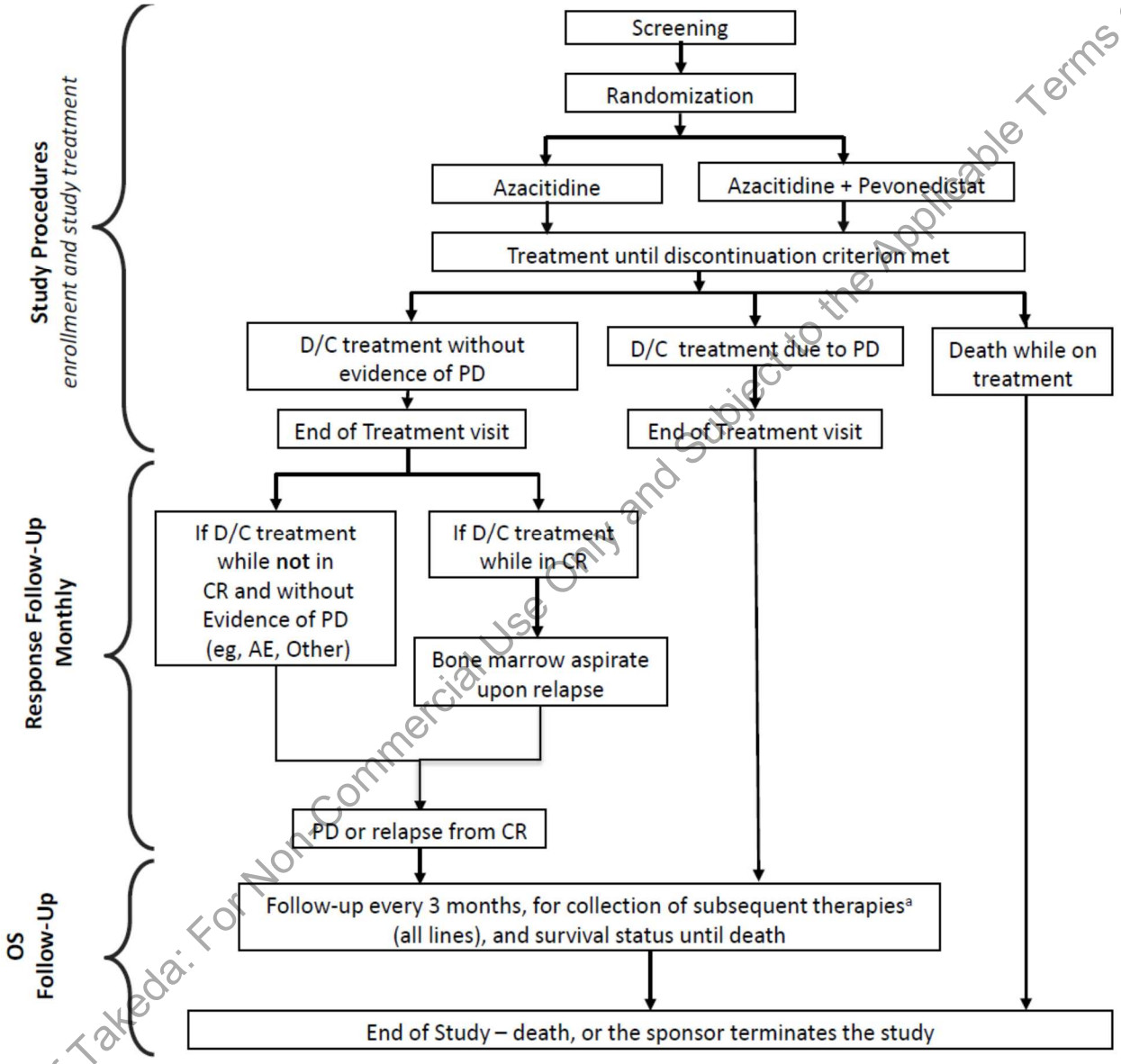
Refer to Section 9.4.20 for response definitions (eg, CR, PR, transformation to AML, PD).

AE=adverse event, AML=acute myelogenous leukemia, CMML=chronic myelomonocytic leukemia, CR=complete remission, D/C=discontinuation (of study treatment), EFS=event-free survival, HMAs= hypomethylating agents, HR MDS=higher-risk myelodysplastic syndromes, OS=overall survival, PD=progressive disease, PR=partial remission, WBC=white blood cell.

(a) Patients who have started subsequent therapy will not be required to have monthly visits but will have a bone marrow aspirate and hematology tests (see Table 9.d) at the time of suspected transformation to AML. Bone marrow aspirate and hematology tests will be sent to the central laboratory.

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

STUDY OVERVIEW DIAGRAM 2:
PATIENTS WITH LOW-BLAST AML



Refer to Section 9.4.20 for response definitions (eg, CR and PD).

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

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

Appendix C Schedule of Events

	Screening (a,b)	Treatment Cycle (28 Days) (c,d,e)											End of Treatment (f)	Follow-up (g)		
		Cycle 1							Cycle 2 and beyond					EFS	Response FU	OS
	Days	1	2	3	5	8	15	21	1	3	5	22		Every month	Every month	Every 3 months
Procedures	**Window**						**±1 day**	**±1 day**				**±10 days**	**+10 days**	**±1 week**	**±1 week**	**±2 weeks**
Informed consent	X															
Inclusion/exclusion (h)	X															
Demographics	X															
Complete medical history and IPSS-R risk categorization (patients with HR MDS or CMML)	X															
Modified Charlson Comorbidity Index assessment (i)	X															
Complete physical examination	X												X			
Symptom-directed physical examination		X							X					X	X	
Height	X															
Weight	X	X(j)							X(j)				X			
ECOG performance status	X								X				X			
Vital signs (k)	X	X		X	X				X	X	X		X			
12-lead ECG (l)	X												X			
Chest x-ray (m)	X															
Pregnancy test (n)	X	X							X				X			
Hematology (o)	X	X		X	X	X	X	X	X				X	X	X	
Coagulation (p)	X															
Complete chemistry panel (o,q)	X	X							X				X	X	X	
Select chemistry panel (o,r)				X	X	X	X	X		X	X					

Footnotes are on last table page.

Appendix C Schedule of Events (continued)

	Screening (a,b)	Treatment Cycle (28 Days) (c,d,e)											End of Treatment (f)	Follow-up (g)		
		Cycle 1							Cycle 2 and beyond					EFS	Response FU	OS
	Days	1	2	3	5	8	15	21	1	3	5	22		Every month	Every month	Every 3 months
Procedures	**Window**						**±1 day**	**±1 day**				**±10 days**	**+10 days**	**±1 week**	**±1 week**	**±2 weeks**
Blood phosphate (s)					X						X					
Reticulocyte count and ferritin (t)	X	X							X				X			
Urinalysis with microscopic analysis (u)	X												X			
EORTC QLQ-C30 and EORTC supplemental items (v)	X	X							X				X	X	X	
EQ-5D-5L (v)	X	X							X				X	X	X	
Hospitalization assessment (v)		X							X				X	X	X	
Plasma samples for pevonedistat PK		X (w)		X (w)	X (w)				X (x)							
Whole blood sample for molecular analysis (y)	X											X				
Buccal epithelial cells sample for DNA	X (z)															
SAE collection (aa)	SAEs including serious pretreatment events will be reported from the time informed consent is signed through 30 days after the last dose of any study drug															
AE collection	X (bb)	Recorded from the first dose of any study drug through 30 days after the last dose of any study drug. TEAEs 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).														
Concomitant medications/therapy		Recorded from the first dose of any study drug through 30 days after the last dose of any study drug														
RBC and platelet transfusion documentation	Recorded from 8 weeks before randomization through 30 days after the last dose of any study drug															
Subsequent therapies (cc)													X	X	X	X
Survival follow-up contact																X

Footnotes are on last table page.

Appendix C Schedule of Events (continued)

	Screening (a,b)	Treatment Cycle (28 Days) (c,d,e)											End of Treatment (f)	Follow-up (g)		
		Cycle 1							Cycle 2 and beyond					EFS	Response FU	OS
	Days	1	2	3	5	8	15	21	1	3	5	22		Every month	Every month	Every 3 months
Procedures	**Window**						**±1 day**	**±1 day**				**±10 days**	**+10 days**	**±1 week**	**±1 week**	**±2 weeks**
Disease Assessment																
Disease assessment based on hematology tests (o,dd)									X				X	X	X	
Disease assessment based on bone marrow aspiration/biopsy	See the Bone Marrow Collection and Assessment Schedule Table A															
Study Drug Administration: Single-Agent Azacitidine or Combination Pevonedistat Plus Azacitidine (e,ee,ff)																
Pevonedistat infusion		Days 1, 3, and 5 of each cycle														
Azacitidine administration		Days 1-5 and 8 and 9 of each cycle														

AE=adverse event, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AML=acute myelogenous leukemia, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BSA=body surface area, BUN=blood urea nitrogen, CMML=chronic myelomonocytic leukemia, DME=drug metabolizing enzymes, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EFS=event-free survival, EOT=end of treatment, HMAs=hypomethylating agents, HRQOL=health-related quality of life, IEC=independent ethics committee, IPSS-R=Revised International Prognostic Scoring System, IRB=institutional review board, IV=intravenous(ly), LDH=lactate dehydrogenase, MDS=myelodysplastic syndromes, OS=overall survival, PK=pharmacokinetic, PT=prothrombin time, RBC=red blood cell, SAE=serious adverse event, SC=subcutaneous(ly), TEAE=treatment emergent adverse events, WBC=white blood cell.

Nonessential protocol visits that do not require on-site sample collection and assessment may be completed via telemedicine (video or phone conversation between the patient and the treating physician, if allowed per Health Authorities, privacy laws, and institutional and local guidelines) in situations where a site visit cannot be conducted, such as in a COVID-19 pandemic.

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

(b) Except for hematology, procedures conducted during the Screening period that are performed within 24 hours of Cycle 1 Day 1 can also be used as the baseline evaluation and do not need to be repeated. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

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

(d) For a new cycle of treatment with study drug(s) to begin, toxicities considered to be related to treatment with study drug(s) must have resolved to the level or grade defined in Section 8.3.1.

(e) The first dose of study drug must be administered within 5 days of randomization on study. It is strongly recommended that dosing for both treatment arms occur on the days specified. However, dosing of either drug may be delayed for safety reasons or other unavoidable circumstances (eg, weather conditions affecting clinic accessibility). If pevonedistat dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained. In each cycle, a maximum of 3 doses of pevonedistat and 7 doses azacitidine (as applicable) should not be exceeded. For the combination arm, pevonedistat and azacitidine should always be administered on the same day (eg, instead of pevonedistat dosing on Days 1, 3, and 5, it would be acceptable to dose on Days 1, 5, and 8). If dosing is adjusted, study procedures should be performed on the actual day of dosing.

(f) The EOT visit will occur 30 days (+10 days) after the last dose of study drug(s) or before the start of subsequent antineoplastic therapy if that occurs sooner. After the EOT visit, patients with HR MDS or CMML will enter EFS follow-up if their disease has not transformed to AML. Patients with low-blast AML will enter response follow-up if their disease has not progressed (as defined in Section 9.4.20) and they have not started subsequent therapy.

(g) Patients with HR MDS or CMML will have EFS follow-up study visits every month if their disease has not transformed to AML and they have not started subsequent therapy. Patients who have started subsequent therapy will not be required to have monthly visits but will have a bone marrow aspirate and hematology tests (samples sent to central laboratory) at the time of suspected transformation to AML or PD (for patients who discontinue treatment without evidenced of PD). Patients with low-blast AML will have response follow-up study visits every month until they relapse from CR or meet the criteria for PD. All patients will enter OS follow-up (contacted every 3 months) when they have confirmed transformation to AML (for patients with HR MDS or CMML at enrollment) or experienced PD or relapse from CR (for patients with low-blast AML at study enrollment).

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

(i) See Appendix L for the Modified Charlson Comorbidity Index.

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

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

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

(m) If a chest x-ray or chest computed tomography scan was performed within 2 months before randomization, the chest x-ray does not need to be performed during Screening.

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

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

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

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

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

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

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

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

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

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

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

(y) Whole blood samples for molecular analysis will be obtained at Screening or anytime before the first administration of study drug, within ±10 days when marrow aspirate for molecular analysis is obtained on Cycle 2, Cycle 4, Cycle 6, Cycle 9, and relapse (see Table A). The 10-day window for collection of this sample allows for it to be obtained along with other blood collection procedures thereby reducing the number of venipunctures. The date and cycle of collection of the blood sample for molecular analysis should be noted on the eCRFs. Whole blood samples will be sent to a central laboratory for molecular analysis.

(z) Buccal epithelial cell samples will be collected for DNA analysis and for genotyping of DME and/or transporter polymorphisms; procedure is specified in the Study Manual.

(aa) SAEs will be entered on the eCRF (see Section 10.2). 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).

(bb) Nonserious pretreatment events related to study screening procedures will be reported from the time of the signing of the ICF up to first dose of study drug and recorded in the eCRFs.

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

(dd) Hematology tests will also be collected at relapse or PD, and as clinically indicated (see Section 9.4.20 for detailed examples).

(ee) Combination Pevonedistat Plus Azacitidine Arm only: see Section 8.1.2 for pevonedistat dosing instructions. On Days 1, 3, and 5 when both study drugs are administered, azacitidine will be administered first followed by pevonedistat. Subsequent pevonedistat doses may be reduced because of toxicity in accordance with Section 8.3.

(ff) All patients will receive azacitidine 75 mg/m^2 IV or SC on Days 1 through 5 (inclusive), Day 8, and Day 9 of each cycle in accordance with Section 8.1.1. The azacitidine dose may be reduced because of toxicity in accordance with Section 8.3.

Table A Bone Marrow Collection and Assessment Schedule

Assessment	Screening	Cycle 2 Day 22 (+6 Days)	Cycle 4 Day 22 (+6 days)	Cycle 6 Day 22 (+6 days)	Cycle 9 Day 22 (+6 days), and Then Every 3 Cycles Thereafter	Relapse(a)	EFS Follow-up	Response Follow-up
Bone marrow blast count *(Local analysis, and central analysis if required)(b)*	X (c)	X (d)	X (d,e)	X (d,e)	X (d,e)	X	X (f)	X (g)
Fresh bone marrow aspirate sample for cytogenetics *(Local and central analyses)* (h)	X(i)	X	X (e)	X (e)	X (e)	X		
Mutation analysis (j) *(Local analysis only)*	X							
Fresh bone marrow aspirate sample for molecular analysis *(Central analysis only)*	X (k)	X (k)	X (e,k)	X (e,k)	X (e,k)	X (l)		

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

(a) Relapse includes the following:

Relapse from CR or PR in patients with HR MDS or CMML.
Relapse from CR in patients with AML.
PD in patients with AML with a PR at end of treatment.

(b) 1 aspirate smear from the local analysis should be submitted to the central laboratory at timepoints where blast counts samples are sent to central laboratory.

(c) A bone marrow biopsy (in addition to bone marrow aspirate) is required only at Screening to confirm the diagnosis but if a bone marrow biopsy is not collected routinely per country institutional guidelines, it is not required. Bone marrow aspirates will be collected at all other time points, at relapse or PD, and as clinically indicated (see Section 9.4.20 for detailed examples). A bone marrow biopsy may be collected with bone marrow aspirate in accordance with institutional guidelines. If a bone marrow aspirate and biopsy were performed within 28 days before randomization, these archival samples may be used to confirm diagnosis and patient eligibility and do not need to be repeated. However, a bone marrow aspirate for molecular analysis is still required at Screening (see footnote i). The bone marrow pathology report(s) will be submitted to the central laboratory. A bone marrow aspirate is required during Screening for bone marrow blast count and will serve as a baseline to assess response. The screening marrow aspirate also is required for central molecular analysis and for local as well as central cytogenetics. If local

cytogenetics was done during the 28 days before randomization and before the screening bone marrow aspirate, it need not be repeated during the screening bone marrow aspirate.

(d) A bone marrow aspirate for blast count (to inform disease burden assessment) will be performed on Day 22 (+6 days) of Cycle 2, Cycle 4, Cycle 6, Cycle 9 and every 3 cycles thereafter. Results must be available before dosing starts in the next cycle.

(e) Following Cycle 4, bone marrow aspirates will be performed only as clinically indicated in patients who achieve CR. Patients who achieve a CR by Cycle 4 are encouraged, but not required to have a bone marrow aspirates on Cycles 6 and 9. Patients with AML who have a CRi are required to have bone marrow aspirates on Cycles 6 and 9.

(f) Patients with HR MDS or CMML not in CR or PR will have bone marrow assessments performed for EFS follow-up at time of suspected PD and at the time of suspected transformation to AML. Additional bone marrow aspirates may be performed if warranted by changes in peripheral blood counts. Patients with HR MDS or CMML who discontinue treatment while in CR or PR will also have a bone marrow aspirate at the time of suspected relapse. Patients who transform to AML after EOT will proceed into OS follow-up.

(g) Patients with low-blast AML who discontinue treatment without evidence of CR and without PD will have a bone marrow aspirate at the time of suspected PD during response follow-up. Patients who discontinue treatment while in CR will also have a bone marrow aspirate performed at the time of suspected relapse. Patients with PD after EOT will proceed into OS follow-up.

(h) Local and central cytogenetics will be performed at Screening. Central cytogenetics will be performed at all other time points noted. Local cytogenetics may also be done at other time points at the site's discretion, but results will not be collected in the eCRF, and cytogenetics report(s) will not be submitted to the central laboratory outside of the requirement during Screening.

(i) Cytogenetics analysis for eligibility will be done locally at the clinical site and will be used to randomize the patient. A bone marrow aspirate sample taken within 28 days of randomization will be tested according to institutional guidelines in a cytogenetics laboratory routinely used by the site. Analyses should be done by karyotype, and by FISH if possible. Results will be collected in the eCRF and the cytogenetics report(s) will be submitted to the central laboratory. Central cytogenetics also will be performed at Screening

(j) Mutation analysis on Screening bone marrow aspirate samples to be performed locally at the clinical site according to institutional guidelines/standard practice (eg, genomic analysis or PCR analysis) and this information will be collected from sites. If mutation analysis is not performed routinely per country/institutional guidelines, it is not required. Results will be collected in the eCRF and the mutation analysis report(s) will be submitted to the central laboratory. Results of mutation analysis if performed within 28 days of randomization may be submitted to the central laboratory.

(k) A fresh bone marrow aspirate obtained at Screening or anytime before the first administration of study drug, will be used for baseline molecular characterization. A bone marrow aspirate sample for molecular analysis will also be obtained when a bone marrow aspirate is done on Day 22 (+6 days) of Cycle 2, Cycle 4, Cycle 6, Cycle 9 and relapse. Bone marrow aspirate samples will be sent to a central laboratory for molecular analysis.

(l) If relapse is suspected, the sample for molecular analysis will be collected at the time the bone marrow sample for disease assessment is collected and sent to the central laboratory (per instructions in the Laboratory Manual). Patients with HR MDS/CMML who relapse from CR or PR (HR MDS/CMML) or patients with low-blast AML who relapse from CR or progress from PR will have fresh bone marrow aspirate sample sent for molecular analysis (Central Analysis).

Appendix D Responsibilities of the Investigator

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

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

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

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

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

Appendix E Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix F ECOG Scale for Performance Status

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

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

ECOG=Eastern Cooperative Oncology Group.

Appendix G Definition of Postmenopausal

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

Appendix H Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective[1]

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

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [2]:
  - oral.
  - Intravaginal.
  - Transdermal.
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
  - oral.
  - Injectable.
  - implantable [3].
- intrauterine device (IUD) [3].
- intrauterine hormone-releasing system (IUS) [3].
- bilateral tubal occlusion [3].
- vasectomised partner [3,4].
- sexual abstinence [5].

Methods that are Considered Less Highly Effective

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

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- male or female condom with or without spermicide [6].
- cap, diaphragm or sponge with spermicide [6].

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

1) If patients are taking oral contraceptives and experience adverse events, such as severe vomiting, that interfere with taking these oral medicines, one of the other highly effective methods of contraception should be used.

2) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

3) Contraception methods that in the context of this guidance are considered to have low user dependency.

4) Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomised partner has received medical assessment of the surgical success.

5) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

6) A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Appendix I Cockcroft-Gault Equation

For male patient/subject:

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

For female patient/subject:

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

Appendix J New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac disease [83].

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

Appendix K CYP3A Inducers

Treatment with any of the strong CYP3A inducers listed in the following table within 14 days before the first dose of pevonedistat was a criterion for exclusion from enrollment in this study. Based on findings from Study P1015, strong CYP3A inducers are not expected to have a clinically meaningful effect on pevonedistat systemic exposures, and as of Amendment 07, administration of these drugs is permitted while on study treatment. Note that HIV medications that are strong CYP3A inducers are not included in this list because HIV-positive patients are excluded from study participation.

In Vivo Inducers of CYP3A

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

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

Appendix L Modified Charlson Comorbidity Index

Modified Charlson Comorbidity Index

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

Source: From Etienne et al, 2007 [84].

Appendix M BSA Calculation

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

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

OR

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

Appendix N Formula for ANC Calculation

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

Example:

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

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

CCI

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	21-Sep-2021 16:34 UTC
	Clinical Science Approval	21-Sep-2021 19:38 UTC
	Biostatistics Approval	22-Sep-2021 02:27 UTC
	Clinical Science Approval	22-Sep-2021 12:13 UTC