Clinical Study Protocol

NCT Number: NCT04266795

Title: A Randomized, Open-label, Controlled, Phase 2 Study of Pevonedistat, Venetoclax, and Azacitidine Versus Venetoclax Plus Azacitidine in Adults With Newly Diagnosed Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy

Study Number: Pevonedistat-2002

Document Version and Date: Version 4.0 (21-January-2022)

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

PROTOCOL

A Randomized, Open-label, Controlled, Phase 2 Study of Pevonedistat, Venetoclax, and Azacitidine Versus Venetoclax Plus Azacitidine in Adults With Newly Diagnosed Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy

Triple Combination of Pevonedistat and Venetoclax Plus Azacitidine in Adults With Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy

Sponsor: Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington, Massachusetts 02421, USA
Telephone: +1 (617) 761-6939

Study Number: Pevonedistat-2002

EudraCT Number: 2019-003117-33

Compound: Pevonedistat (TAK-924/MLN4924)

Date: 21 January 2022 **Version/Amendment Number** 4

Amendment History:

Date	Amendment No.	Amendment Type	Region
21 January 2022	4	Substantial	Global
08 July 2021	3	Substantial (not implemented)	Global
28 July 2020	2	Substantial	Global
10 July 2020	1	Substantial	Global
21 November 2019	Initial Protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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

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

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.

The names and contact information for the Medical Monitor and Responsible Medical Officer are in the Study Manual. For SAE and pregnancy reporting, see Section 10.0.

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

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

[redacted] MD Date
(or designee)

[redacted] PhD Date
Statistical and Quantitative Sciences
(or designee)

INVESTIGATOR AGREEMENT

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

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

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 4 Summary of Changes

Protocol Amendment 4 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 4.

The primary reasons for this amendment are to modify the statistical design and schedule of assessments/procedures, given emerging data from the pevonedistat program.

Results of the registration-enabling Study Pevonedistat-3001 (PANTHER), 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, became available in September 2021. The primary endpoint of event-free survival (EFS) was not met and no statistically significant benefits were observed with pevonedistat treatment. As such, Takeda will not pursue further development of pevonedistat in any indication.

On the basis of these results, the Pevonedistat-2002 Protocol Amendment 4 contains the following key design changes:

- Remove the interim analysis (IA) to evaluate EFS for futility and event size re-estimation.
- Update the timing for the final analysis (FA).
- Provide guidance for modification of the study procedures and assessments for patients who remain on study treatment.
- Update several secondary objectives and endpoints.
- Remove the Independent Review Committee (IRC) assessment of disease evaluation data.
- Remove Independent Data Monitoring Committee (IDMC) evaluations of the safety and efficacy data.

Protocol Amendment 3 (dated 08 July 2021), which converted the phase 2 study to a registration-enabling phase 3 study and included a change in the primary endpoint, expansion of sample size, and increase in number of sites, will not be implemented. Thus, the changes described below for the current Protocol Amendment 4 are relative to Protocol Amendment 2 (dated 28 July 2020) rather than Protocol Amendment 3.

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

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol Amendment 2			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 Study Summary Section 13.1.3.4 Multiplicity Control (deleted) Section 13.2 IA and Event Size Re-estimation Section 13.3 Determination of Sample Size	Modified the statistical analysis for primary and secondary endpoints by removing the interim analysis (IA) and event-size re-estimation.	Changes made to align the statistical analysis with the current expected data.
2.	Appendix A Modified Schedule of Events and throughout the document where it is referenced. Appendix L Schedule of EventsSchedule of Events and throughout the document where it is referenced.	Provided a modified SOE for patients continuing treatment after implementation of Protocol Amendment 4. Moved the original (Protocol Amendment 2) SOE from Appendix A to Appendix L for reference purposes.	Changes made to reduce data collection and lessen patient burden and to more closely align with clinical practice.
3.	Section 2.0 Study Summary Section 5.1.2.2 Other Secondary Objectives Section 5.2.2.2 Other Secondary Endpoints Section 6.1 Overview of Study Design Table 6.a Primary and Secondary Endpoints for Disclosures Section 9.4.23 Patient Reported Outcomes (deleted) Section 9.4.24 Hospitalization Assessment (deleted) Section 9.10 Posttreatment Follow-up Assessments (EFS, Response, and OS) Section 13.1.3.3 Analyses of Other Secondary Efficacy Endpoints Section 13.1.6 Patient-Reported Outcomes (deleted)	Removed the secondary objectives and endpoints relating to: • 6-month, 1-year, and 2-year survival rates. • Duration of composite complete remission (CCR), complete remission + partial recovery of blood cells (CR + CRh), and overall response rate (ORR). • Determination of time to relapse from CR/complete remission with incomplete blood count recovery (CRi), or death, whichever occurs first. • Failure to achieve CR or CRi at completion of 6 treatment cycles, relapse from CR/CRi or death from any cause, whichever occurs first. • Health-related quality of life (HRQOL) assessments. • Red blood cell (RBC) and platelet transfusion	Relevant data for analysis are not expected due to discontinuation of the study.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol Amendment 2			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		independence rates and duration for each treatment arm. • Comparison of hospitalization rates for patients in each treatment arm.	
4.	Section 2.0 Study Summary Table 6.a Primary and Secondary Endpoints for Disclosures Section 6.3 Duration of Study Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting Section 6.3.4 Total Study Duration Section 6.3.5 Early Discontinuation of the Study	Updated the period of evaluation up to approximately 3 years. Added sponsor's decision as a reason for early discontinuation of the study.	Change made to reflect the current expected timeframe for study completion
5.	Section 2.0 Study Summary Section 6.1 Overview of Study Design Table 6.a Primary and Secondary Endpoints for Disclosures Section 8.8 Blinding and Unblinding Section 11.1 IRC (deleted) Section 13.1.3.1 Analyses for Primary Efficacy Endpoint Section 13.1.3.3 Analyses of Other Secondary Efficacy Endpoints	Revised text to indicate the evaluation of disease for primary and secondary endpoints will be based on investigator assessment; independent review committee (IRC) assessment will no longer be required.	Since the study is being terminated by the sponsor, investigator assessment of efficacy is sufficient.
6.	Section 8.8 Blinding and Unblinding Section 13.1.1 Analysis Sets (Per Protocol Population) Section 14.1 Study-Site Monitoring Visits	Removed the requirement that the sponsor and sponsor's staff are to be blinded to treatment assignment.	Removed blinding to increase efficiency of statistical data analysis
7.	Section 11.2 Independent Data Monitoring Committee (deleted)	Removed independent data monitoring committee (IDMC) evaluations.	A separate evaluation by the IDMC is no longer necessary because the sponsor will be unblinded,.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol Amendment 2			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
8.	Section 2.0 Study Summary Section 9.6 Completion of Study (for Individual Patients) Section 9.8 Withdrawal of Patients From Study Section 9.11 Posttrial Access Section 9.12 Duration of PTA	Updated and clarified text on the posttrial access (PTA) program and its duration.	Change made to reflect the current approach to be taken by the sponsor.
9.	Section 2.0 Study Summary Section 6.1 Overview of Study Design Section 9.4.18 Clinical Laboratory Evaluations Section 9.4.18.1 Clinical Chemistry, Hematology, and Urinalysis Section 9.4.19 Disease Assessment	Revised to indicate that local laboratories will be used following implementation of Protocol Amendment 4.	Change made as central laboratory evaluations are no longer required.
10.	Section 9.6 Completion of Study (for Individual Patients) Section 9.8 Withdrawal of Patients From Study	Added study termination by the sponsor as a reason for study completion.	Change made to provide guidance and clarify reasons for study completion.
11.	Section 13.1.3.1 Analyses for Primary Efficacy Endpoint	Removed language regarding data censorship and planned subgroup and sensitivity analyses for event-free survival (EFS).	These EFS analyses are no longer applicable since the IRC assessment has been removed.
12.	Section 14.1 Study-Site Monitoring Visits	Provided alternative monitoring visit approaches such as remote source data verification (SDV).	Change made to provide general guidance for SDV to be performed remotely during the coronavirus disease 2019 (COVID-19) pandemic.
13.	Section 8.3.1.3 Venetoclax Dosing With CYP3A4 Inducers and Inhibitors	Removed isavuconazole from the list of cytochrome P450 (CYP)3A inhibitor.	Isavuconazole is not a CYP3A inhibitor and was included in error.
14.	Section 8.10 Preparation, Reconstitution, and Dispensing	Added normal saline (0.9% sodium chloride) solution as a diluent for pevonedistat.	Change made to add an additional diluent for pevonedistat dose preparation.
15.	Section 8.2 Reference/Control Therapy: Venetoclax Plus Azacitidine	Clarified that body surface area (BSA) should be measured in both treatment arms.	Provided missing information for the reference/control therapy.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol Amendment 2			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
16.	Section 9.4.20 Biomarker, Pharmacodynamic, and PK Samples Section 9.4.21 PK Measurements	Updated the location of instructions for pharmacokinetic (PK) sample collection.	Change made to clarify location of instructions.
17.	Section 9.4.2 Reconsent of Patients	Updated text to include a subsection for patient reconsent following implementation of Protocol Amendment 4.	Added to ensure that patients continuing on study after implementation of Protocol Amendment 4 will be reconsented.
18.	Section 13.1.5 Pharmacodynamic Analysis	Updated text to add flexibility to data analyses.	Change made to include the sponsor's revised data analysis approach.
19.	Section 6.3.6 Posttrial Access (section deleted)	Deleted redundant text.	PTA information is also in Section 9.11; thus, duplicate information in Section 6.3.6 has been deleted.
20.	Section 8.3.4 Criteria for Discontinuation of Study Drug (section deleted)	Deleted redundant text.	Discontinuation criteria are also included in Section 9.7; thus, duplicate information in Section 8.3.4 has been deleted.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. (TDCA)	**Compound:** Pevonedistat (TAK-924; MLN4924)
Title of Protocol: A Randomized, Open-label, Controlled, Phase 2 Study of Pevonedistat, Venetoclax, and Azacitidine Versus Venetoclax Plus Azacitidine in Adults With Newly Diagnosed Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy	**EudraCT No**.: 2019-003117-33
Study Number: Pevonedistat-2002	**Phase:** 2

Study Design:

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

It is expected that approximately 150 patients with newly diagnosed acute myeloid leukemia (AML) will be enrolled in this study. At enrollment, patients will be randomized at a 1:1 ratio to receive (either pevonedistat + venetoclax + azacitidine [Arm A] or venetoclax + azacitidine [Arm B]) in 28-day treatment cycles. Patients will be stratified by age (18 to <75 years; ≥75 years) and AML subtype (de novo AML; secondary AML). Secondary AML (sAML) is defined as AML after myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN), or therapy-related AML (t-AML) following cytotoxic therapy, and/or radiotherapy for a malignant or nonmalignant disease.

Patients, including those who achieve complete remission (CR) or complete remission with incomplete blood count recovery (CRi), may receive study treatment until they experience unacceptable toxicity, relapse, or progressive disease (PD) as defined in this study. Patients 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 the patient is still receiving clinical benefit from the treatment, based on the clinical judgment of the investigator, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients who continue in the study under these conditions must be reconsented before continuing to receive study treatment. Patients may choose to discontinue treatment at any time.

Patients will attend the end-of-treatment visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner. Patients who discontinue study treatment without evidence of PD will enter event-free survival (EFS) follow-up and have study visits every month for assessments inclusive of physical examination, clinical blood tests, and upon relapse from CR or CRi, and bone marrow aspirate (BMA) sampling. Patients will enter overall survival (OS) follow-up (contacted every 3 months to document subsequent therapies and survival status) when they have relapsed from CR or CRi, failed to achieve CR or CRi, or started subsequent therapy. The Modified Schedule of Events (Appendix A) will be followed upon implementation of Protocol Amendment 4. Long-term follow up visits (EFS/response and OS) will no longer be required; patients will complete an End of Treatment visit 30 (+10) days after the last dose of study drug(s) or before the start of antineoplastic therapy if that occurs sooner.

Disease response assessments will be based on the 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 [1]. Formal disease assessments for study endpoints will be determined based on local BMA blast counts and transfusions, and central laboratory data. Disease response assessments will be carried out by the investigator. BMA samples will be collected at screening, during treatment, and during follow-up for blast count evaluation (to inform disease burden assessment). BMAs also will be used to analyze tumor cytogenetics, to analyze baseline somatic mutations and other molecular characteristics, to assess impact of therapy on depth and durability of response at predetermined time points using molecular techniques, and to identify treatment emergent mutations. Samples will be collected and analyzed from patients in both treatment arms. After implementation of Protocol Amendment 4, there will be no follow-up period and collection of BMA samples will not be required, except

as indicated per standard of care.

Sparse sampling for the determination of pevonedistat plasma concentrations will be collected from each patient in the investigational arm pevonedistat + venetoclax + azacitidine (Arm A) to contribute to a population pharmacokinetics (PK) analysis of pevonedistat co-administered with venetoclax and azacitidine.

Adverse events and Eastern Cooperative Oncology Group (ECOG) performance status will be assessed; electrocardiograms, clinical laboratory values, and vital signs measurements will be obtained, to evaluate the safety and tolerability of the study drug treatments.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective 27 November 2017 [2].

Primary Objective:

The primary objective of the study is to determine whether the combination of pevonedistat + venetoclax + azacitidine improves EFS compared with venetoclax + azacitidine in patients with newly diagnosed AML who are unfit for intensive chemotherapy. EFS is defined as the time from study randomization to the date of failure to achieve CR/CRi (ie, discontinuing treatment without achieving CR/CRi), relapse from CR or CRi, or death from any cause, whichever occurs first [3].

Secondary Objectives:

Key Secondary Objective: To determine whether the combination of pevonedistat + venetoclax + azacitidine improves OS when compared with venetoclax + azacitidine in patients with newly diagnosed AML who are unfit for intensive chemotherapy.

Other Secondary Objectives:

- To assess 30- and 60-day mortality rates in both treatment arms.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine improves the rate of CR, composite complete remission (CCR [CR + CRi]), overall response rate (ORR [CR + CRi + partial remission (PR)]), CR + partial recovery of blood cells (CRh); and leukemia response rate (CR + CRi + PR + morphological leukemia-free state [MLFS, marrow CR (mCR)]), compared with venetoclax + azacitidine.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine improves duration of CR and CRi compared with venetoclax + azacitidine.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine shortens time to first CR, CRi, or PR when compared with venetoclax + azacitidine.
- To collect plasma concentration-time data for pevonedistat in combination with venetoclax + azacitidine to contribute to the future population PK and exposure response (safety/efficacy) analyses of pevonedistat.

Patient Population: Adults with newly diagnosed AML who are unfit for treatment with intensive chemotherapy.

Number of Patients:	**Number of Sites:**
Approximately 150 patients will be randomized in a 1:1 ratio to receive either the investigational combination of pevonedistat + venetoclax + azacitidine (Arm A) or the control arm of venetoclax + azacitidine (Arm B).	Approximately 85 sites globally.
Dose Level(s): The treatment cycle for both arms in the study is 28 days. **Investigational Arm (Arm A):** • Pevonedistat (20 mg/m^2, IV infusion) on Days 1, 3, and 5 PLUS • Venetoclax (400 mg) on Days 1 through 28 in Cycle 1. Ramp-up (Cycle 1 only): venetoclax will be	**Route of Administration:** Pevonedistat: intravenous (IV) infusion. Venetoclax: oral administration. Azacitidine: IV or subcutaneous (SC), per investigator's choice.

administered at a dose of 100 mg on Day 1; 200 mg on Day 2; thereafter, at 400 mg on Days 3 through 28. Venetoclax (400 mg) on Days 1 through 28 of a 28-day cycle at Cycle 2 and beyond. If remission is confirmed in Cycle 1 or thereafter, Venetoclax (400 mg) can be administered on Days 1 through 21 of a 28-day cycle in subsequent cycles, to prevent potential prolonged myelosuppression and treatment delays. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles. PLUS • Azacitidine (75 mg/m^2, IV or SC) on Days 1 through 7 **or** Days 1 through 5, 8, and 9. **Control Arm (Arm B):** • Venetoclax (400 mg) on Days 1 through 28 in Cycle 1. <u>Ramp-up (Cycle 1 only):</u> venetoclax will be administered at a dose of 100 mg on Day 1; 200 mg on Day 2; thereafter, at 400 mg on Days 3 through 28. Venetoclax (400 mg) on Days 1 through 28 of a 28-day cycle at Cycle 2 and beyond. If remission is confirmed in Cycle 1 or thereafter, Venetoclax (400 mg) can be administered on Days 1 through 21 of a 28-day cycle in subsequent cycles, to prevent potential prolonged myelosuppression and treatment delays. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles. PLUS • Azacitidine (75 mg/m^2, IV or SC) on Days 1 through 7 **or** Days 1 through 5, 8, and 9.	
Duration of Treatment: Patients, including those who achieve CR, may receive study treatment until they experience unacceptable toxicity, relapse, or experience PD as defined in this study. Patients 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 the patient is still receiving clinical benefit from the treatment, based on the clinical judgment of the investigator, and the continuation is endorsed by the sponsor's project clinician (or designee). Patients may choose to discontinue treatment at any time.	**Period of Evaluation:** Up to approximately 3 years.

Posttrial Access: Where permitted by local regulations, and if the responsible investigator and the sponsor agree that the patient would derive benefit from or would be harmed without continued access to the assigned treatment regimen, patients may continue to receive access to the assigned treatment regimen after the study is completed. If a posttrial access (PTA) program should become an option for a patient, then pevonedistat + venetoclax + azacitidine or venetoclax + azacitidine, depending on treatment arm assignment, may be provided through the PTA program.	

Main Criteria for Inclusion:

- Male or female patients aged ≥18 years with newly diagnosed AML, morphologically confirmed (World Health Organization [WHO] criteria 2008). Patients may have newly diagnosed primary de novo AML or secondary AML (sAML) defined as AML after myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN), or therapy-related AML (t-AML) following cytotoxic therapy, and/or radiotherapy for a malignant or nonmalignant disease.
- To qualify for this study, a patient must be considered to be unfit for treatment with a standard Ara-C and anthracycline induction regimen due to age or co-morbidities defined by 1 of the following:
  ≥75 years of age
  OR
  ≥18 to <75 years of age with at least one of the following:
  - ECOG performance status of 2 or 3.
  - Severe cardiac disorder (eg, congestive heart failure requiring treatment, ejection fraction ≤50%, or chronic stable angina).
  - Severe pulmonary disorder (eg, carbon monoxide lung diffusion capacity ≤65% or forced expiratory volume in 1 second ≤65%).
  - Creatinine clearance <45 mL/min (but ≥30 mL/min as part of general eligibility criteria).
  - Hepatic disorder with total bilirubin >1.5 times the upper limit of the normal range (ULN).
- 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):
  - Total bilirubin ≤1.5 times ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll with direct bilirubin ≤3 times the ULN of the direct bilirubin. Elevated indirect bilirubin due to posttransfusion hemolysis is allowed.
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 times the ULN.
  - Creatinine clearance ≥30 mL/minute (calculated by the Modification of Diet in Renal Disease Study equation).
  - Albumin >2.7 g/dL.
- White blood cell count (WBC) $<25 \times 10^9$/L. Patients who are cytoreduced with leukapheresis or with hydroxyurea may be enrolled if they meet the eligibility criteria before starting therapy.

Main Criteria for Exclusion:

- History of myeloproliferative neoplasm with BCR-ABL1 translocation or AML with BCR-ABL1 translocation.
- Genetic diagnosis of acute promyelocytic leukemia.
- Extramedullary AML without evidence of bone marrow involvement.
- Prior treatment with hypomethylating agents for AML (treatment with hypomethylating agents for prior myelodysplastic syndromes [MDS] is not exclusionary).
- Eligible for intensive chemotherapy and/or allogeneic stem cell transplantation.
- Patients with either clinical evidence of or history of central nervous system involvement by AML.
- Diagnosed or treated for another malignancy (except for adequately-treated carcinoma in situ of any organ or nonmelanoma skin cancer) within 1 year before randomization or previously diagnosed with another malignancy and have any evidence of residual disease that may compromise the administration of pevonedistat, venetoclax or azacitidine. Prior MDS is also allowed, but the patient cannot have received treatment for MDS within 14 days before first dose of any study drug.
- Patient has a WBC count $\geq 25 \times 10^9$/L.
- Patient with known hypersensitivity to pevonedistat, venetoclax, or azacitidine, and/or their excipients.
- Uncontrolled HIV infection.
- Patient is known to be positive for hepatitis B or C infection, with the exception of those with an undetectable viral load within 3 months.
- Known hepatic cirrhosis.
- Treatment with strong cytochrome P450 (CYP)3A4 inducers within 14 days before the first dose of the study drug.
- Patients with the following will be excluded: uncontrolled intercurrent illness including, but not limited to known cardiopulmonary disease defined as unstable angina, clinically significant arrhythmia, congestive heart failure (New York Heart Association Class III or IV), and/or ST elevation myocardial infarction within 6 months before first dose, or severe symptomatic pulmonary hypertension requiring pharmacologic therapy, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
- Patient who has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, or cardiovascular disease that, in the medical judgement of the investigator, may compromise the delivery of pevonedistat, venetoclax, and/or azacitidine.
- Patients with uncontrolled coagulopathy or bleeding disorder.

Main Criteria for Evaluation and Analyses:

Primary Endpoint: The primary endpoint of the study is EFS. EFS is defined as the time from study randomization to the date of failure to achieve CR/CRi (ie, discontinuing treatment without achieving CR/CRi), relapse from CR or CRi, or death from any cause, whichever occurs first [3].

Key Secondary Endpoint: The key secondary endpoint is OS.

Other Secondary Endpoints:

- 30- and 60-day mortality rates.
- Disease response rates: CR; CCR (CR + CRi); ORR (CR + CRi + PR); CR + CRh (CRh is defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts [platelets >50,000/µL and absolute neutrophil count >500/µL]); and leukemia response rate (CR + CRi + PR + MLFS [mCR]).
- Duration of CR and CRi.
- Time to first CR, CRi, and PR.
- Pevonedistat plasma concentration-time data.

Statistical Considerations:

The study was originally designed to have approximately 85 EFS events to provide 80% power to detect a hazard ratio (HR) of 0.58 (median EFS of 19 months in the investigational pevonedistat + venetoclax + azacitidine arm [Arm A] versus 11 months in the venetoclax + azacitidine control arm [Arm B], assuming exponential distribution of EFS), using stratified log-rank test at one-sided 5% significance level. One interim analysis (IA) was planned in the original design. Following decisions and changes made within the pevonedistat program after read-out from Study Pevonedistat-3001, the IA was removed. Instead, final analysis (FA) will be conducted after Pevonsdistat-2002 Protocol Amendment 4 is implemented. Study enrollment was complete with 164 patients randomized.

Sample Size:

Approximately 150 patients will be randomized in a 1:1 ratio to receive either the combination of pevonedistat + venetoclax + azacitidine or venetoclax + azacitidine.

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 supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

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

3.3 List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BH3	BCL-2 homology
BMA	bone marrow aspirate
BSA	body surface area
BUN	blood urea nitrogen
CCR	composite complete remission
CDL	cullin-dependent ubiquitin E3 ligases
CFR	Code of Federal Regulations
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CMML	chronic myelomonocytic leukemia
COVID-19	coronavirus disease 2019
CR	complete response; complete remission
CrCl	creatinine clearance
CRh	complete remission + partial recovery of blood cells (CRh is defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts [platelets >50,000/μL and absolute neutrophil count >500/μL])
CRi	complete remission with incomplete blood count recovery
CRL	cullin-RING ligase
CRO	contract research organization
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer

EORTC-QLQ	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire
EOT	end-of-treatment
EQ 5D-5L	EuroQoL 5 dimensions 5 levels (a standardized instrument for measuring generic health status)
EU	European Union
FA	final analysis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practices
HNSTD	highest nonseverely toxic dose
HR	hazard ratio
HR MDS	higher-risk MDS
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplant
IA	interim analysis
IB	Investigator's Brochure
IC	intensive chemotherapy
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDH2	isocitrate dehydrogenase 2
IDMC	independent data monitoring committee
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
IWRS	interactive web response system
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
LFT	liver function test
mCR	marrow complete remission
MDRD	Modification of Diet in Renal Disease
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Healthcare products Regulatory Agency
MLFS	morphological leukemia-free state
MOA	mechanism of action

MPN	myeloproliferative neoplasm
MRD	minimal residual disease
MRP2	multidrug resistance-associated protein 2
MTD	maximum tolerated dose
MUGA	multigated acquisition
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
NOXA	BH3-only protein involved in regulating cell death decisions
OATP	organic anion-transporting protein
ORR	overall response rate
OS	overall survival
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PP	Per-protocol
PR	partial response, partial remission
PRO	patient-reported outcome
PT	Preferred Term
PTA	posttrial access
PTE	pretreatment event
Q	intercompartmental distributional clearance
QTc	corrected QT interval
RBC	red blood cell
RFS	relapse-free survival
SAE	serious adverse event
sAML	secondary acute myeloid leukemia
SAP	statistical analysis plan
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
t-AML	therapy-related AML
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
UK	United Kingdom
ULN	upper limit of the normal range
UPS	ubiquitin-proteasome system
US	United States
USPI	US prescribing information

Vc	central volume
Vp	peripheral volume
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

TDCA	Takeda Development Center Americas, Inc

4.0 INTRODUCTION

4.1 Background

4.1.1 Scientific Background

4.1.1.1 Disease Under Treatment

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by the infiltration of the bone marrow, blood, and, occasionally, other organs by clonal and often highly proliferative, abnormally/poorly differentiated hematopoietic cells termed myeloblasts [6]. There is enormous cytogenetic and molecular heterogeneity within AML, which greatly impacts prognosis [6]. AML is curable in approximately 40% of younger adults (<60 years of age) but only in about 10% of patients 60 years of age or older, whose median survival has historically been less than a year [6] but appears to be improving with the advent of combination regimens involving newer, targeted therapies [7-10]. Increasing age is associated with factors predictive of early death, for example, poor performance status or various comorbidities, and of treatment resistance, for example, adverse cytogenetics, secondary AML, or the multidrug-resistant phenotype [3]. AML has conventionally been treated with intensive chemotherapy (IC), including an anthracycline and cytarabine; however, IC often cannot be safely administered to older patients. With the use of IC, complete remission (CR) rates range from 60% to 80% among younger adults [3]. In fit, older patients able to receive IC, CR rates are around 50%. Unfortunately, relapse of AML is common, except in certain genetically defined subsets, and the 5-year overall survival (OS) of patients with relapsed AML is exceedingly poor (no more than approximately 10%). Recent therapeutic advances, eg, the isocitrate dehydrogenase 2 (IDH2) inhibitor enasidenib (Idhifa), may have improved the outlook for a minority of patients [11].

4.1.1.2 Study Drug: Pevonedistat

Pevonedistat (also known as TAK 924 and MLN4924; hereinafter referred to as pevonedistat) is a first-in-class, small molecule inhibitor of neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)-activating enzyme (NAE) under development for the treatment of malignancies. The NEDD8 conjugation (neddylation) pathway is responsible for much of the regulated protein turnover in the cell, which is similar to the ubiquitin-proteasome system (UPS). However, UPS is known to regulate myriad processes in eukaryotic cells, whereas only a limited number of neddylation substrates have been described to date. Bortezomib for injection, a drug that acts by inhibiting the 26S proteasome, has proven utility in the treatment of multiple myeloma and mantle cell lymphoma. Therefore, it is anticipated that other compounds directed against different components of the UPS and/or the NEDD8 conjugation pathway may prove useful in the treatment of malignancies. NAE, E1 ligase, is an essential component of the NEDD8 conjugation pathway, which initiates the neddylation to protein substrates. Specifically, NEDD8 conjugation to cullin-dependent ubiquitin E3 ligases (CDLs) is necessary for their activity. The ligases in the NEDD8 conjugation pathway control the timely neddylation of many substrate proteins with important roles in cell cycle progression and signal transduction. The ubiquitination/neddylation

of proteins targets them for proteasomal degradation. These cellular processes are relevant to tumor cell growth, proliferation, and survival; as such, inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers by inhibiting the degradation of a subset of proteins that are regulated by the proteasome. In nonclinical studies, treatment of cells with pevonedistat results in the accumulation of CDL substrates, followed by a DNA damage response and cell death. Pevonedistat treatment results in tumor growth inhibition in mouse tumor xenograft models of solid tumors, lymphoma, and AML.

4.2 Nonclinical Experience

The pharmacologic profile of pevonedistat has been thoroughly characterized in vitro and in vivo. These studies demonstrate that pevonedistat is a potent, reversible, and selective mechanism-based inhibitor of NAE activity. Pevonedistat inhibited viability of a wide variety of tumor cell lines and showed antitumor activity when administered as a single-agent and in combination with other treatments in immunocompromised xenograft-bearing mice.

Pevonedistat has an acceptable nonclinical absorption, distribution, metabolism, and excretion profile. Plasma clearance varied in nonclinical species, and plasma half-life varied from 1 hr in rats to 15 hours in monkeys. Pevonedistat was highly bound in whole blood and plasma of mice, rats, dogs, monkeys, and humans. No metabolite unique to humans was observed in vitro. In vitro, pevonedistat is predominantly metabolized by the cytochrome P450 (CYP)3A4. However, a clinical drug-drug interaction (DDI) study (C15011) conducted for pevonedistat in combination with a strong CYP3A4/P-glycoprotein (P-gp) inhibitor, itraconazole, did not show any clinically meaningful change in the pevonedistat exposure. Pevonedistat is neither an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC_{50} >100 μM and K_i >50 μM) nor an inducer of CYP1A2, 2B6, or 3A4/5 (at up to 30 μM) but is a weak inhibitor of CYP2B6 and 2C8 (IC_{50} = 97.6 and 23.1 μM, respectively). The major elimination pathway of pevonedistat in animals is through the hepatic route. Pevonedistat is a substrate of P-gp, breast cancer resistance protein (BCRP), and multidrug resistance-associated protein 2 (MRP2) in Caco-2 cells. Pevonedistat is also a weak inhibitor of P-gp (IC_{50} = 41.2 to 56.0 μM) and BCRP (IC_{50} = 6.3 μM) but not of MRP2 (IC_{50} >200 μM). Additionally, pevonedistat is not a substrate for organic anion-transporting proteins (OATPs).

Findings in the GLP-compliant, definitive toxicity studies in Sprague-Dawley rats and beagle dogs generally were comparable and predominantly related to the pharmacologic effects (or sequelae thereof) of pevonedistat. The primary dose-limiting toxicities (DLTs) in both species were considered to be gastrointestinal (GI) injury with electrolyte and hydration perturbations and complications linked with bone marrow and lymphoid tissue depletion. Additionally, an acute phase-like response was observed in both species and consisted of alterations in body temperature, increased serum fibrinogen, decreased serum albumin, alterations in circulating neutrophils, and in dogs, increased neutrophil infiltration in multiple tissues. Cardiovascular effects in the dog and rat were also noted and consisted of decreased blood pressure (mean and systolic), increased heart rate, and shortened partial response (PR) and QT intervals followed by an increased diastolic blood pressure. In rats, increased blood pressure was noted 24 hours postdose. The highest nonseverely toxic dose (HNSTD) (administered cyclically) was 15 mg/kg (300 mg/m^2) in dogs and 60 mg/kg (360 mg/m^2) in rats. At the HNSTD, the most sensitive indicators of pevonedistat-related effects in

both species included GI tract functional perturbations (emesis [dogs only] and abnormal excreta), hematologic alterations, and acute phase response (increased fibrinogen and decreased albumin). The primary pevonedistat-related effects are considered to be monitorable and reversible. Toxicity (cardiopulmonary effects, renal changes, and hepatic injury) noted at higher doses in rats (≥120 mg/kg) appeared to be correlated with sepsis.

Pevonedistat was not mutagenic in the bacterial reverse mutation assay (Ames assay). In a combined micronucleus test and comet assay study in Sprague-Dawley rats, pevonedistat induced chromosome damage in immature erythrocytes in the bone marrow micronucleus test and showed evidence of DNA damage in the liver in the comet assay. Based on the mechanism of action of pevonedistat (DNA re-replication) and following biological effects on the cell cycle, these findings are not unexpected.

Microscopic changes were observed in male and female reproductive organs in repeat-dose toxicology studies (including vacuolation, degeneration, and necrosis of the seminiferous tubules of the testes and luminal cellular debris in the epididymides of both rats and dogs, incomplete corpora lutea in rats, and neutrophilic infiltrates in the ovary in dogs); therefore, pevonedistat likely represents a reproductive hazard. In a non-GLP compliant embryo-fetal development study in Sprague-Dawley rats (daily subcutaneous [SC] doses of 0, 5, 15, 30, and 45 mg/kg on gestation days 6 to 17), pevonedistat at ≥15 mg/kg resulted in maternal and/or fetal toxicity (including maternal decreased food consumption, postimplantation loss, decreased fetal body weights, external and skeletal fetal malformations); no maternal or fetal toxicity was observed at 5 mg/kg.

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

4.3 Clinical Experience

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

- Study C15001 in patients with solid tumors.
- Study C15002 in patients with lymphoma or multiple myeloma.
- Study C15003 in patients with AML, high-grade myelodysplastic syndromes (MDS), or acute lymphoblastic leukemia.
- Study C15005 in patients with melanoma.

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

Beyond the first four phase 1 studies, an approximate 436 additional patients have been treated with pevonedistat in single-agent and combination studies, and no Cycle 1 Day 1 SAEs as previously described have been observed. These patients received pevonedistat at a dose of 50 to 100 mg/m^2 as a single-agent, a dose of 15 to 30 mg/m^2 in combination with different standard of care therapies, or a dose of 8 mg/m^2 to 20 mg/m^2 in combination with a CYP3A inhibitor.

As of 22 January 2019, a total of 647 patients are estimated to have received at least 1 dose of pevonedistat in the overall clinical development program. Fourteen clinical studies include the previously mentioned 4 monotherapy studies. Current development is focused on pevonedistat in combination with standard clinically available therapies in hematologic malignancies and solid tumors. These studies in patients with advanced malignancies are as follows:

- Combination therapy of pevonedistat + standard of care in patients with solid tumors:
  - C15010 (phase 1b) is complete: evaluated the maximum tolerated dose (MTD) of pevonedistat plus docetaxel, gemcitabine, or the combination of carboplatin and paclitaxel.
  - C15011 (phase 1) is complete: evaluated the effects of fluconazole and itraconazole CYP3A-mediated inhibition (DDI) on the pharmacokinetics (PK), safety, and tolerability of pevonedistat.
  - Pevonedistat-1013 (phase 1) is complete: Part A assessed the mass balance, PK, and metabolism of [^{14}C]-pevonedistat, and Part B evaluated the efficacy of pevonedistat in combination with docetaxel or the combination of carboplatin and paclitaxel.
  - Pevonedistat-1014 (phase 1) is ongoing: Part A (enrollment is complete) is evaluating the effects of pevonedistat on the corrected QT (QTc) interval. Part B is evaluating the efficacy of pevonedistat in combination with docetaxel or the combination of carboplatin and paclitaxel.
  - Pevonedistat-1015 (phase 1) is ongoing: Part A (enrollment is complete) is evaluating the effects of rifampin (DDI) on PK of pevonedistat. Part B is evaluating the efficacy of pevonedistat in combination with docetaxel or the combination of carboplatin and paclitaxel.
- Combination therapy of pevonedistat + azacitidine in patients with hematologic malignances:
  - C15009 (phase 1b) is complete: The study established the MTD of pevonedistat in combination with azacitidine and assessed the safety and tolerability of the combination in treatment-naïve patients with AML ≥60 years.

    For patients treated with pevonedistat 20 mg/m^2 and azacitidine 75 mg/m^2 (total: N = 61), most common treatment-emergent adverse events (TEAEs) in Study C15009 were constipation (48%), followed by fatigue and nausea (both 42%), anemia (41%), febrile neutropenia and thrombocytopenia (both 31%), decreased appetite (30%), pyrexia (27%), and neutropenia, diarrhea, and vomiting (25% each). Three patients received pevonedistat 30 mg/m^2 and azacitidine 75 mg/m^2; 2 patients each event had an adverse event (AE) of thrombocytopenia, pneumonia, alanine aminotransferase (ALT) increased, blood creatinine increased, aspartate aminotransferase (AST) increased, and blood alkaline

phosphatase (ALP) increased. All other AEs in this treatment group were experienced by 1 patient for each event.

Overall, responses of CR, complete remission with incomplete blood count recovery (CRi), and PR were observed in 31 out of 61 (51%) of patients treated at the MTD (20 mg/m^2) of the safety population and 31 out of 52 patients (60%) of patients in the MTD response-evaluable population.

- Pevonedistat-1012 (phase 1/1b) is complete: evaluated the safety and tolerability of the pevonedistat monotherapy and the combination of pevonedistat + azacitidine in adult East Asian population with AML or MDS; determined the recommended phase 2/3 doses of the combination; and characterized the PK of the monotherapy and the combination.

  In the single-agent pevonedistat arm (N = 10), the most common TEAEs were pneumonia (7 patients [70%]), febrile neutropenia (6 patients [60%]), and constipation, nausea, stomatitis, insomnia (all 4 patients [40%] each). In the combination arm (N = 13), the most common TEAEs were constipation (9 patients [69%]), vomiting (7 patients [54%]), back pain (6 patients [46%]), and nausea and anemia (5 patients [38%] each).

  Overall, 6 (31.6%) of 19 patients in the response-evaluable population of the study (pevonedistat single-agent or in combination with azacitidine) achieved a response (CR, CRi, or PR for patients with AML; CR, PR, hematologic improvement, or marrow complete remission [mCR] for patients with higher-risk [HR] MDS).

- Pevonedistat-1016 (phase 1/1b) is ongoing: The study is enrolling patients with HR MDS, chronic myelomonocytic leukemia (CMML), and AML who have severe renal or mild hepatic impairment. The objectives of the study are to determine the PK (of pevonedistat), disease response, safety, and MTD (of the combination therapy) for this population.
- Pevonedistat-2001 (phase 2) is ongoing (enrollment is complete): The primary objective of the study is to assess whether the combination of pevonedistat + azacitidine versus the azacitidine monotherapy improves event-free survival (EFS) in a patient population with HR MDS, CMML, and AML.
- Pevonedistat-3001 (phase 3) is ongoing: The study is being conducted to assess efficacy and safety of pevonedistat + azacitidine, versus the monotherapy azacitidine, as a first-line treatment for patients with HR MDS, CMML, and AML. The primary endpoint is overall response rate (ORR) by Cycle 6 and the key secondary endpoint is EFS.

4.4 PK

Population PK analysis was conducted using data from pevonedistat single-agent studies (C15001, C15002, C15003, and C15005) and pevonedistat in combination with standard of care chemotherapy (C15009 and C15010) in patients with solid tumor or hematologic malignancies. The database contained 335 patients contributing 3768 PK observations. Pevonedistat plasma concentration-time profiles were well described by a 2-compartment model with linear elimination. Body surface area (BSA) was an important predictor of clearance (CL), intercompartmental distributional clearance (Q), and both central and peripheral volumes (Vc and Vp, respectively).

For a typical patient with a BSA of 1.73 m^2, an alpha half-life of 1.27 hours and a beta (elimination) half-life of 7.85 hours are estimated. Concurrent administration of carboplatin and paclitaxel decreased the CL of pevonedistat by approximately 44%, translating to an approximately 80% higher pevonedistat exposure area under the plasma concentration-time curve (AUC) during co-administration with carboplatin and paclitaxel, consistent with pevonedistat concentration data observed in Study C15010. Co-administration with azacitidine, gemcitabine, or docetaxel did not appear to affect pevonedistat exposures. Race, sex, age, tumor type (hematologic vs solid), mild or moderate renal impairment (creatinine clearance [CrCl] ≥30 mL/min), and mildly impaired liver function (ie, total bilirubin ≤ upper limit of the normal range [ULN] and ALT/AST ≤2.5 times the ULN), had no impact on pevonedistat PK.

An open-label DDI Study C15011 evaluated the CYP3A-mediated inhibitory effects of fluconazole and itraconazole on pevonedistat PK in patients with advanced solid tumors. The results indicated that itraconazole, a strong CYP3A/P-gp inhibitor, and fluconazole, a moderate CYP3A inhibitor, had no clinically meaningful effects on pevonedistat PK.

For detailed information please consult the current IB.

4.5 Pharmacodynamics

As detailed in Section 4.2, nonclinical studies have identified specific pathways that are modulated by NAE inhibition in cultured cells and animal models. Several specific pharmacodynamic assays have been developed to track the biological consequences of NAE inhibition in patient tumor, skin, and blood, such as immunohistochemistry analysis of CDT1 and NRF2 levels as well as upregulation of NRF2 dependent transcripts. A total of 8 NRF2 dependent genes were identified in preclinical studies as induced by pevonedistat-mediated NAE inhibition: *ATF3*, *GCLM*, *GSR*, *MAG1*, *NQO1*, *SLC7A11*, *SRXN1*, and *TXNRD1*. Increases in these 8 genes have been demonstrated following ex vivo dosing of human whole blood with pevonedistat and following treatment of cell lines with pevonedistat and, therefore, represent a pharmacodynamic marker downstream of NAE inhibition. Analysis of patient samples from pevonedistat clinical studies provide evidence of pathway inhibition downstream of NAE and biological activity of pevonedistat in whole blood, skin, and tumor tissue (solid tumor or AML bone marrow–derived blasts) at all doses tested in pharmacodynamic assays. These doses range from 15 to 261 mg/m^2 across various single-agent, phase 1 pevonedistat trials, including the monotherapy studies (C15001, C15002, C15003, C15005) and study C15011 (DDI study). Analysis of postdose tumor and skin samples demonstrated an increase in expression of CDT1 and/or NRF2 consistent with stabilization of these proteins following decreased CDL activity consequent to NAE inhibition by pevonedistat. However, substantial heterogeneity was observed between patients in the degree of CDT1 and NRF2 induction in both tumor and skin tissues, with no apparent correlation between pevonedistat dose and observed fold change. Across studies (C15001, C15002, C15003, C15005, and C15011), gene expression analysis done on peripheral blood mononuclear cells identified NQO1 and SLC7A11 as the genes with the largest and most consistent increases among all 8 NAE-regulated transcriptional targets analyzed. These data support the use of these 2 genes as appropriate pharmacodynamic markers of pevonedistat activity going forward.

Inhibition by venetoclax efficiently disrupts Bcl-2 signaling in cells and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent human tumor cell lines (NDA 208573: Pharmacology Review, 26 March 2016). This include induction of cytochrome C release and cl. caspase activation. In addition, venetoclax had no effect on the viability of BAX-/-BAK-/-MEFs cells, indicating that these Bcl-2 family effectors are required for the cell killing activity of this Bcl-2–selective inhibitor. In this study, pharmacodynamic assessment will be performed to determine changes in the relative expression levels of BCL2, BCLXL, MCL1, BAX, BAK, and apoptosis-related proteins between pre- and posttreatment bone marrow aspirate (BMA) or peripheral blood samples in both bulk leukemia and leukemic stem/progenitor cells. As mentioned in Section 4.6.2, myeloid leukemia cell differentiation protein (MCL-1, a pro-survival Bcl-2 family member) upregulation is thought to be a primary mode of resistance to venetoclax. Preclinical studies suggest that pevonedistat may work to prevent venetoclax resistance through degradation of MCL-1. In addition, pevonedistat inhibits NEDD8-activating enzyme, thereby preventing ubiquitination of c-Myc (and other proteins). Elevated c-Myc causes transactivation of proapoptotic factors like BCL-2 homology 3 (BH3)-only protein involved in regulating cell death decisions (NOXA). NOXA neutralizes prosurvival proteins like MCL-1 and subsequently leads to activation of the pro-apoptotic proteins BAX and BAK, leading to a lowered threshold to apoptosis and thereby maintaining sensitivity to venetoclax and navitoclax. Importantly, NOXA knockdown provides substantial protection from pevonedistat-induced apoptosis in AML lines [12]. Therefore MCL-1, c-Myc, NOXA, BAX and BAK may represent pharmacodynamic biomarkers in the combination of pevonedistat and venetoclax.

For detailed information please consult the current IB.

4.6 Rationale for the Proposed Study

Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of BCL-2 and has shown promising anti-leukemia activity in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) as monotherapy and modest single-agent activity in select subtypes of AML [13-15]. Venetoclax is currently United States (US) Food and Drug Administration (FDA) approved for the treatment of patients with CLL with del(17)(p13.1) and for patients with AML, in combination with either low-dose cytarabine or hypomethylating agents (eg, azacitidine or decitabine) [4,16].

The combination of venetoclax + hypomethylating agents is emerging as a new standard of care for older patients with newly diagnosed AML who are unfit for standard intensive chemotherapy [4]. Venetoclax, in combination with either decitabine or azacitidine, is being studied in an ongoing clinical trial to evaluate the safety and efficacy of the respective combinations [17] in patients with untreated AML who are ≥65 years of age and unfit for chemotherapy. Beginning with a short ramp-up phase of venetoclax to the target dose, patients received venetoclax at a dose of 400 mg, 800 mg, or 1200 mg daily, along with standard dosing of decitabine intravenous (IV) (20 mg/m^2 × 5 days) or azacitidine IV/SC (75 mg/m^2 × 7 days). To date, 145 patients with a median age of 74 years (range, 65 to 86 years) have been treated. For 49% of patients, cytogenetics were a poor risk, and 25% of patients had secondary AML (sAML) (either after MDS/myeloproliferative neoplasm [MPN] or with prior chemotherapy). Nausea (43%),

thrombocytopenia (38%), neutropenia (34%), and decreased white blood cell (WBC) count (26%) were the most common AEs related to the venetoclax treatment. The CR/CRi rate for the entire cohort was 66% with a median duration of CR/CRi of 11.0 months. In the subgroup of patients with secondary AML, the CR/CRi rate was 65%. The 30-day and 60-day mortality rates were 3% and 8%, respectively. The median OS for the entire cohort was 17.5 months (95% CI, 12.3 months to upper limit not reached). For older, unfit patients with newly diagnosed AML these results represent the best survival data reported to date. Emerging clinical and exposure response data suggest that the 400 mg dose of venetoclax has the best benefit-risk profile. A phase 3 study of venetoclax at a treatment dose of 400 mg plus azacitidine is ongoing.

4.6.1 Rationale for the Study Population

AML is the most common form of acute leukemia in adults. Despite advances in the management of hematologic malignancies, the development of novel targeted and immune therapies, and improvements in supportive care, the overall outcome for patients with AML remains poor. This prognosis can be attributed to several factors, which include increased frequency in an older population, poor response to chemotherapy, high relapse rates, and limited effective therapy options for patients who have relapsed. Many patients with AML are not candidates for standard induction therapy; therefore, strategies to increase duration of response or reduce relapse in this patient population are needed. Development of new therapies for patients with AML, who are unfit for induction therapy, remains an important unmet clinical need.

A phase 1/2 study (University of Texas MD Anderson Cancer Center) of pevonedistat in combination with azacitidine plus venetoclax in patients with secondary AML (sAML) is ongoing.

4.6.2 Rationale for the Combination of Pevonedistat Plus Venetoclax in Patients With AML

Hematologic malignancies are highly dependent upon the antiapoptotic protein BCL-2 for survival. Overexpression of BCL-2 is associated with tumor initiation, disease progression, and drug resistance and is thus a compelling target for antitumor therapy. BCL-2 family proteins mediate an intrinsic, mitochondrial apoptosis pathway. BCL-2, BCL-XL, and MCL-1 are antiapoptotic BCL-2 family proteins that keep the cell alive, while BH3 proteins BIM, BID, BAD, NOXA, PUMA, and HRK are pro-apoptotic BCL-2 family proteins that trigger cell death.

Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of BCL-2 that binds with >1000-fold higher affinity for BCL-2 than for BCL-XL or MCL-1 [18]. Venetoclax has shown promising antileukemia activity in patients with previously untreated as well as relapsed or refractory CLL as monotherapy and modest single-agent activity in select subtypes of AML [13,18,19]; venetoclax is currently approved by the FDA for the treatment of patients with CLL with or without del(17)(p13.1).

There is notable preclinical rationale for the combination of venetoclax with pevonedistat in the treatment of AML. In one study, pevonedistat was shown to exert synergistic cytotoxic effect when combined with Bcl-2 inhibitors such as venetoclax or navitoclax [12,20]. This was likely mediated indirectly by pevonedistat-induced accumulation of the cullin-RING ligase (CRL)

substrate c-MYC. c-MYC activates the PMAIP1 gene that encodes for NOXA, leading to increased NOXA protein, subsequent BAX and BAK activation, and apoptosis. Because NOXA neutralizes Mcl-1, which is an established resistance mechanism for patients treated with venetoclax-based regimens [21,22], the combination of venetoclax with pevonedistat may help to prevent resistance to venetoclax and therefore prolong duration of response.

The combination of venetoclax with either low-dose cytarabine [4,16] or hypomethylating agents (eg, azacitidine or decitabine) [9,14] was recently approved by the FDA under accelerated approval and is emerging as a new standard of care for older patients with newly diagnosed AML who are unfit for standard intensive chemotherapy.

4.6.3 Therapeutic Rationale for the Combination of Pevonedistat, Venetoclax and Azacitidine in Patients With AML

Pevonedistat is a first-in-class, small molecule inhibitor of NAE, which catalyzes the rate-limiting step in the process of attachment of NEDD8 to CRLs, an important class of E3 ubiquitin ligases [23]. Inhibiting protein neddylation is a more selective way of inhibiting protein degradation than global proteasome inhibition [24]. In AML cell lines and primary specimens, pevonedistat treatment stabilized key NAE targets, inhibited nuclear factor kappa B activity, and induced DNA damage and reactive oxygen species generation [25]. In a comprehensive protein profiling study using a FLT3-ITD + AML cell line, 47 proteins were significantly up-regulated following pevonedistat treatment, mostly established cullin-dependent substrates [26]. Only 36% (17/47) of these proteins were also pharmacodynamically increased by pevonedistat treatment of melanoma cells, suggesting that protein modulation by pevonedistat may be tumor type-dependent. Azacitidine antagonizes ribonucleotide reductase, which is induced by pevonedistat, and the combination was found to synergize in induction of apoptosis of a variety of AML cell lines via this mechanism [26]. These findings were recapitulated in a FLT3-ITD + AML xenograft model. In a phase 1 clinical trial of pevonedistat monotherapy in patients with relapsed/refractory AML or MDS (n = 72), single-agent activity was observed, with achievement of CR in 2 patients and PR in 2 patients receiving pevonedistat IV on Days 1, 3 and 5 of a 21-day cycle, and PR in 2 patients receiving the drug on Days 1, 4, 8, and 11 of a 21-day cycle [27].

Following this signal, a phase 1 study of pevonedistat in combination with azacitidine was conducted in 61 patients ≥60 years of age with previously untreated AML [19]. Patients were required to have at least 1 feature that made them poor candidates for IC; these included age ≥75 years, history of an antecedent hematologic disorder, adverse karyotype or an Eastern Cooperative Oncology Group (ECOG) performance status of 2. The combination was well-tolerated, and the recommended phase 2 dose was established at 20 mg/m^2/day of pevonedistat, administered on Days 1, 3 and 5, in combination with 75 mg/m^2/day of azacitidine, administered on Days 1 through 5, 8, and 9, of a 28-day cycle. The ORR was 60% among 52 evaluable patients, of whom 26 (43%) patients had secondary AML. There were no meaningful differences between the response rates (ORR, CR, Cri, and PR rates) between patients with de novo AML and secondary AML; however, there was a trend towards improved OS among the patients with secondary AML (median, 11.2 months vs 5.6 months for de novo AML, 7 months for the whole cohort). The median duration of remission was 8.3 months. 61% of the responses

occurred by Cycle 2, and 90% by Cycle 4. Interestingly, 6 of 9 patients with TP53 mutations responded (3 CR/CRi, 3 PR) with a median duration of 8.46 months; 4 of the 9 patients remained on study for >10 cycles. Concurrent administration of azacitidine did not affect the PK of pevonedistat.

On the basis of the clinical benefit observed with pevonedistat + azacitidine [19], improved efficacy of venetoclax in AML when combined with azacitidine [4], and preclinical evidence of synergy between venetoclax and pevonedistat [12,20], it is thought that combination therapy with pevonedistat + venetoclax + azacitidine may result in improved outcomes compared with either combination alone in patients with newly diagnosed AML who are unfit for standard intensive chemotherapy.

4.6.4 Rationale for Dose and Schedule of Study Drugs

The selection of pevonedistat doses for this study was based on Study C15009, which established the MTD of pevonedistat as 20 mg/m2 given on Days 1, 3, and 5, in combination with azacitidine 75 mg/m2 given on Days 1 through 5, 8, and 9, in 28-day treatment cycles. In this study, azacitidine will be administered on 75 mg/m2 on Days 1 through 7, or Days 1 through 5, 8, and 9, the dose regimen of azacitidine in an ongoing phase 1/2 study (University of Texas MD Anderson Cancer Center) of pevonedistat in combination with azacitidine plus venetoclax. The recommended dose in the ongoing study is pevonedistat 20 mg/m2 on Days 1, 3, and 5 in combination with azacitidine at 75 mg/m2 for 7 days plus venetoclax 400 mg daily in 28-day treatment cycles. If remission is confirmed in Cycle 1 or thereafter, Venetoclax (400 mg) can be administered on Days 1 through 21 of a 28-day cycle in subsequent cycles, to prevent potential prolonged myelosuppression and treatment delays. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles.

4.7 Potential Risks and Benefits

4.7.1 Pevonedistat

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

4.7.1.1 Potential Risks From Phase 1 Studies

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

- Multi-organ failure that could result in death in the setting of an acute phase response.

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

4.7.1.2 Potential Risks Confounded by Underlying Disease or Malignancy

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

- Fatigue.
- Chills.
- Decreased appetite.
- Neutropenia.
- Anemia.
- Thrombocytopenia.
- Febrile neutropenia.
- GI bleeding.
  - All events were assessed by the investigator as unrelated; the majority occurred in the setting of thrombocytopenia.
- Multi-organ failure in the setting of infection.

4.7.1.3 Potential Risks Primarily Based on Findings From Animal Studies

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

- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.

- Cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure, and increased diastolic blood pressure.
- Enteropathy (including dehydration and electrolyte loss) with secondary sepsis.
- Effects on the testes and ovaries that represent a reproductive hazard including sterility.
- Increased developmental risk to the fetus or embryo.
- Decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, high). This finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the doses.
- Prolongation of the activated partial thromboplastin time (aPTT).
- Local tissue injury when administered SC.

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

For detailed information, please consult the current IB.

4.7.1.4 Additional Safety Considerations

Cycle 1 Day 1 Toxicity/Multi-Organ Failure

A comprehensive review of the clinical trial safety data has shown that Cycle 1 Day 1 toxicity involving multi-organ failure, including SAEs of renal, hepatic, and cardiac failure, some with a fatal outcome, has been observed in phase 1, single-agent pevonedistat studies at doses equal to or above 110 mg/m^2.

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

Nonclinical investigative activities were undertaken to better understand the potential physiology behind the Cycle 1 Day 1 events observed with pevonedistat dosing. A model in which a minimally toxic, single dose of pevonedistat was administered with tumor necrosis factor alpha had several hallmarks associated with septic and/or cytokine-induced shock. The overall time course and target organs affected in this nonclinical model also appeared to closely mimic those observed in clinical Cycle 1 Day 1 events at single-agent doses ranging from 110 to 278 mg/m^2.

In October 2012, a revised risk mitigation strategy limiting the dose to no higher than 50 mg/m^2 for dosing on Days 1, 3, and 5 and no higher than 100 mg/m^2 for dosing on Days 1, 4, 8, and 11 or 1, 8, and 15 for all studies for single-agent administration was implemented across the pevonedistat program. As of January 2019, approximately 436 additional patients have been treated with pevonedistat in single-agent and combination studies, and no Cycle 1 Day 1 SAEs as described above have been observed. These patients received pevonedistat at a dose of 50 to 100 mg/m^2 as a

single-agent, a dose of 15 to 30 mg/m^2 in combination with different standard of care therapies, or a dose of 8 to 20 mg/m^2 in combination with a CYP3A inhibitor.

The schedule for pevonedistat infusion of Days 1, 3, and 5 was chosen for further studies.

Increases in Serum Creatinine

At doses equal to or below 50 mg/m^2 on a Days 1, 3, and 5 schedule or below 100 mg/m^2 on a Days 1, 4, 8, and 11 schedule, there have been reports of changes in serum creatinine from baseline levels of Grade 0 to Grade 1, and from baseline levels of Grade 1 to Grade 2.

Increases in Liver Enzymes and Biochemical Tests

Grade 1 to Grade 4 increases in AE related to liver function analyses (such as for liver transaminases [up to Grade 4], bilirubin [up to Grade 3], and ALP [up to Grade 3]), have been noted following administration of pevonedistat in patients with advanced malignancies receiving pevonedistat as a single-agent and in combination with standard of care cytotoxic therapies. Among the single-agent studies, a Grade 4 AE occurred that was related to liver function (ALT increased). In Study C15009, in patients with AML treated with pevonedistat in combination with azacitidine, Grade 4 increases for AEs related to liver function analyses occurred as DLTs (ALT increased, AST increased), except for 1 event that was not assessed as a DLT (AST increased). In Study C15010 in patients with solid tumors treated with pevonedistat in combination with docetaxel, gemcitabine, or carboplatin plus paclitaxel, and also in Study C15011, a DDI study, AEs related to liver function analyses up to Grade 3 were observed.

Drug Interactions and Other Forms of Interactions

The risk of DDIs between pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data.

In vitro, pevonedistat is metabolized via hydroxylation and oxidation, predominantly by CYP3A4 with a small contribution from CYP2D6 (approximately 3%). An open-label DDI study, C15011, evaluated the CYP3A-mediated inhibitory effects of fluconazole and itraconazole on pevonedistat PK in patients with advanced solid tumors. The results indicated that itraconazole, a strong CYP3A/P-gp inhibitor, and fluconazole, a moderate CYP3A inhibitor, had no clinically meaningful effects on pevonedistat PK. On the basis of these findings, use of CYP3A/P-gp inhibitors in patients receiving pevonedistat is permitted. Strong CYP3A inducers are prohibited for patients receiving pevonedistat. For individual studies in the pevonedistat clinical program, reference should be made to the respective protocols for specific information relating to excluded and permitted medications.

In vitro, pevonedistat does not inhibit the activities of CYP1A2, 2C9, 2C19, 2D6, and 3A4/5, but weakly and reversibly inhibits both CYP2B6 and 2C8; it does not induce CYP1A2, 2B6, and 3A4/5. Thus, pevonedistat is not expected to affect the PK of drugs that are metabolized by these CYP enzymes.

Pevonedistat is also a substrate for the drug efflux transporters, P-gp and BCRP, and a weak inhibitor of P-gp and BCRP-mediated transport. Known BCRP inhibitor (ie, cyclosporine) is currently excluded, but limited use is permitted only if clinically necessary and no suitable alternative exists in clinical studies of pevonedistat. Additional in vitro transport studies showed that pevonedistat is not a substrate of the hepatic OATP, but it can inhibit OATP-mediated uptake of E3S and simvastatin and lovastatin from some donors. On the basis of these data and the recommended clinical dose range, pevonedistat is unlikely to affect the PK of other drugs that are known P-gp, BCRP, or OATP substrates, while the potential exists, albeit low, for drug interactions with BCRP inhibitors.

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.

4.7.2 Venetoclax

An ongoing study is evaluating the safety and efficacy of venetoclax in combination with either decitabine or azacitidine [17]. Enrolled patients are ≥65 years of age with previously untreated AML and who are ineligible for chemotherapy. After a short ramp-up phase of venetoclax to the target dose, patients received venetoclax at a dose of 400 mg, 800 mg, or 1200 mg daily, along with standard dosing of decitabine IV (20 mg/m^2 × 5 days) or azacitidine IV/SC (75 mg/m^2 × 7 days). At the most recent update, 145 patients have been treated with a median age of 74 years (range, 65 to 86 years). Cytogenetics were a poor risk in 49% of patients, and 25% of patients have secondary AML (either after MDS/MPN or with prior chemotherapy). The most common AEs related to venetoclax were nausea (43%), thrombocytopenia (38%), neutropenia (34%), and decreased WBC count (26%). The 30-day and 60-day mortality rates were 3% and 8%, respectively. The CR/CRi rate for the entire cohort was 66% with a median duration of CR/CRi of 11.0 months. In the subgroup of patients with secondary AML, the CR/CRi rate was 65%. The median OS for the entire cohort was 17.5 months (95% CI, 12.3 months to upper limit not reached). These results represent the best survival data for older, unfit patients with newly diagnosed AML yet reported. Emerging clinical and exposure response data have suggested that the 400 mg dose of venetoclax has the best benefit-risk profile, and a phase 3 study of venetoclax 400 mg with azacitidine is ongoing.

Most Commonly Occurring Adverse Reactions (>10%): Neutropenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting, constipation, fatigue, pyrexia, peripheral edema, hypokalemia, headache and cough.

Most Commonly Occurring Laboratory Abnormalities (>10%): Hyperkalemia and hyperphosphatemia.

4.7.2.1 Warnings and Precautions

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in previously treated CLL patients with high tumor burden when treated with venetoclax. Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (CrCl <80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and antihyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors and P-gp inhibitors increases venetoclax exposure, may increase the risk of TLS at initiation and during ramp-up phase and may require venetoclax dose adjustment.

Neutropenia

Grade 3 or 4 neutropenia occurred in 41% (98 out of 240) of patients treated with venetoclax. Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including anitmicrobials for signs of infection and use of growth factors (eg, granulocyte-colony stimulating factor [G-CSF]).

Immunization

Do not administer live attenuated vaccines before, during, or after treatment with venetoclax until B cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied. Advise patients that vaccinations may be less effective.

Embryo-Fetal toxicity

Given its mechanism of action and findings in animals, venetoclax may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in postimplantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant women using venetoclax. Advise females of reproductive potential to avoid pregnancy during treatment. If venetoclax is used during pregnancy or if the patient becomes pregnant while taking venetoclax, the patient should be apprised of the potential hazard to the fetus.

4.7.2.2 Use in Specific Populations

Renal Impairment

Patients with reduced renal function (CrCl <80 mL/min) are at increased risk of TLS. These patients may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with venetoclax.

No specific clinical trials have been conducted in patients with renal impairment. Less than 0.1% of radioactive venetoclax was detected in urine. No dose adjustment is needed for patients with mild-moderate renal impairment (CrCl >30 mL/min) based on the results of population PK analysis. A recommended dose has not been determined for patients with severe renal impairment (CrCl <30 mL/min) or patients on dialysis.

Hepatic Impairment

No specific clinical trials have been conducted in patients with hepatic impairment; however, human mass balance study showed that venetoclax undergoes hepatic elimination. Although no dose adjustment is recommended in patients with mild or moderate hepatic impairment based on results of a population PK analysis, a trend for increased AEs was observed in patients with moderate hepatic impairment; monitor these patients more closely for signs of toxicity during the initiation and dose ramp-up phase. A recommended dose has not been determined for patients with severe hepatic impairment.

4.7.2.3 Drug Interactions

Venetoclax is predominantly metabolized by CYP3A4/5.

Strong CYP3A Inhibitors

Concomitant use of venetoclax with strong CYP3A inhibitors (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole and voriconazole) at initiation and during the ramp-up phase is contraindicated. However, CYP3A4 inhibitors may be used to manage antifungal prophylaxis with “azole” therapy in neutropenic patients (refer to Section 8.3.1.3 and Table 8.d for further details).For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used concomitantly with strong CYP3A inhibitors (refer to Section 8.3.1.3 for further details). Resume the venetoclax dose that was used before initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

Co-administration of ketoconazole increased venetoclax maximum observed plasma concentration (C_{max}) by 2.3-fold and AUC by 6.4-fold.

Moderate CYP3A Inhibitors and P-gp Inhibitors

Avoid concomitant use of moderate CYP3A inhibitors (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil) or P-gp inhibitors (eg, amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor) with venetoclax.

Consider alternative treatments. If a moderated CYP3A inhibitor or a P-gp inhibitor must be used, reduce the venetoclax dose by at least 50% (refer to Section 8.3.1.3 for further details). Monitor patients more closely for signs of venetoclax toxicities.

Resume the venetoclax dose that was used before initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

Avoid grapefruit products, Seville oranges, and starfruit during treatment with venetoclax as they contain inhibitors of CYP3A.

Co-administration of a single dose of rifampin, a P-gp inhibitor, increased venetoclax C_{max} by 106% and AUC by 78%.

CYP3A Inducers

Avoid concomitant use of venetoclax with strong CYP3A inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort) or moderate CYP3A inducers (eg, bosentan, efavirenz, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction.

Co-administration of multiple doses of rifampin, a strong CYP3A inducer, decreased venetoclax C_{max} by 42% and AUC by 71%.

Effects of Venetoclax on Other Drugs

Warfarin: An 18% to 28% increase in warfarin C_{max} and AUC of R and S-warfarin is noted after single doses of venetoclax and warfarin. International normalized ratio (INR) needs to be monitored closely.

P-gp Substrates: In vitro data suggest venetoclax has inhibition potential on P-gp substrates at therapeutic dose levels in the gut. Therefore, co-administration of narrow therapeutic index P-gp substrates (eg, digoxin, everolimus, and sirolimus) with venetoclax should be avoided. If one must be used, administer at least 6 hours before dosing with venetoclax.

4.7.2.4 PK

Following multiple oral doses under fed conditions, the maximum plasma concentration of venetoclax was reached 5 to 8 hours after dosing. AUC increased dose proportionally over the dose range of 150 to 800 mg.

When given with a low-fat meal, venetoclax exposure increased by approximately 3.4-fold and with a high-fat meal, increased by 5.1- to 5.3-fold compared with fasting conditions. Venetoclax should be administered with a meal.

Venetoclax is highly protein bound. The mean blood-to-plasma ratio was 0.57. Volume of distribution ranged from 256 to 321 L in patients.

The terminal elimination half-life is approximately 26 hours.

After a single oral administration of 200 mg radiolabeled (^{14}C)-venetoclax dose, >99.9% is recovered in the feces with <0.1% in the urine within 9 days. Hepatic elimination is the primary route of clearance.

Based on population PK analyses, age, race, sex, and weight do not have a clinically meaningful effect on venetoclax clearance.

4.7.3 Azacitidine

Most Commonly Occurring Adverse Reactions (SC or IV Route): Nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia.

Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (SC or IV Route): Patient discontinuation because of leukopenia, thrombocytopenia, or neutropenia; dose held for leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, or febrile neutropenia; dose reduced for leukopenia, neutropenia, or thrombocytopenia.

In clinical studies, adverse reactions to azacitidine were qualitatively similar between the IV and SC routes of administration. 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.

4.7.3.1 Warnings and Precautions

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.

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. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

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. Renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L), developed in 5 patients with chronic myelogenous leukemia treated with azacitidine and etoposide. Because elderly patients are more likely to have decreased renal function, select the dose carefully and monitor renal function.

In patients with cancer, the PK of azacitidine in 6 patients with normal renal function (CrCl >80 mL/min) and 6 patients with severe renal impairment (CrCl <30 mL/min) were compared following daily SC dosing (Days 1 through 5) at 75 mg/m^2/day. Severe renal impairment increased azacitidine exposure by approximately 70% after single and 41% after multiple SC administrations. This increase in exposure was not correlated with an increase in AEs. The exposure was similar to exposure in patients with normal renal function receiving 100 mg/m^2. Therefore, a Cycle 1 dose modification is not recommended.

However, if unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, reduce the dosage by 50% for the next course. Similarly, if unexplained elevations of blood urea nitrogen (BUN) or serum creatinine occur, delay the next cycle until values return to normal or baseline and reduce the dose by 50% for the next course.

TLS

Azacitidine may cause fatal or serious TLS. TLS may occur despite concomitant use of allopurinol. Assess baseline risk, monitor, and treat as appropriate.

Embryo-Fetal Risk

Based on the mechanism of action and findings in animals, azacitidine can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal dose approximating 8% of the recommended human daily dose caused fetal death and anomalies.

DDIs

No formal clinical drug interaction studies with azacitidine have been conducted. An in vitro study of azacitidine incubation in human liver fractions indicated that azacitidine may be metabolized by the liver. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied. An in vitro study with cultured human hepatocytes indicated that azacitidine at concentrations up to 100 µM (IV C_{max} = 10.6 µM) does not cause any inhibition of CYP2B6 and CYP2C8. The potential of azacitidine to inhibit other CYP enzymes is not known. In vitro studies with human cultured hepatocytes indicate that azacitidine at concentrations of 1.0 µM to 100 µM does not induce CYP 1A2, 2C19, or 3A4/5.

PK

The PK of azacitidine were studied in 6 patients with MDS following a single 75 mg/m^2 SC dose and a single 75 mg/m^2 IV dose. Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/mL occurred in 0.5 hour. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes. The AUC and C_{max} of SC administration of azacitidine in 21 patients with cancer were approximately dose proportional within the 25 to 100 mg/m^2 dose range. Multiple dosing at the recommended dose-regimen does not result in drug accumulation. Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following SC administration of ^{14}C-azacitidine was 50%. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after IV and SC administrations, about 4 hours. The effects of hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied.

4.7.4 Summary of Risks and Benefits

While there is notable preclinical rationale for the combination of venetoclax with pevonedistat in the treatment of AML as noted in Section 4.6.2, this is the first controlled, comparative study by the sponsor in which there will be exposure to humans with the triple combination of pevonedistat, venetoclax, and azacitidine. Pevonedistat has been studied with Bcl-2 inhibitors, such as venetoclax or navitoclax [12], showing synergistic cytotoxic effects. The combination of pevonedistat with azacitidine has been shown to be tolerated in previous studies (ie, C15009 and Pevonedistat-1012). The addition of venetoclax may result in additional adverse effects, which are either different from those typically seen with pevonedistat and azacitidine regimens or occurring at a higher frequency, eg, neutropenia, diarrhea, nausea, upper respiratory tract infections, fatigue, musculoskeletal pain, edema, and cough.

The ORR of pevonedistat in combination with azacitidine has been shown in a phase 1 study (C15009) in patients with untreated AML not suitable for induction therapy to be 60% of the 52 evaluable patients (51% in intent-to-treat [ITT] population) [19]. It is postulated that the addition of venetoclax to a regimen of pevonedistat plus azacitidine will improve OS and/or increase the rate and duration of CR and/or shorten the time to response in patients with AML. Combining pevonedistat with venetoclax may help to prevent resistance to venetoclax and therefore prolong the duration of response in this population with an unmet medical need.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of the study is to determine whether the combination of pevonedistat + venetoclax + azacitidine improves EFS compared with venetoclax + azacitidine in patients with newly diagnosed AML who are unfit for intensive chemotherapy. EFS is defined as the time from study randomization to the date of failure to achieve CR/CRi (ie, discontinuing treatment without achieving CR/CRi), relapse from CR or CRi, or death from any cause, whichever occurs first [3].

5.1.2 Secondary Objectives

5.1.2.1 Key Secondary Objective

The key secondary objective is to determine whether the combination of pevonedistat + venetoclax + azacitidine improves OS when compared with venetoclax + azacitidine in an unfit population of patients with AML.

5.1.2.2 Other Secondary Objectives

Other secondary objectives are:

- To assess 30- and 60-day mortality rates in both treatment arms.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine improves the rate of CR, composite complete remission (CCR [CR + CRi]), ORR (CR + CRi + PR), CR + partial recovery of blood cells ([CRh], and leukemia response rate (CR + CRi + PR + morphological leukemia-free state [MLFS, mCR]), compared with venetoclax + azacitidine.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine improves duration of CR and CRi, compared with venetoclax + azacitidine.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine shortens time to first CR, CRi, or PR when compared with venetoclax + azacitidine.
- To collect plasma concentration-time data for pevonedistat in combination with venetoclax + azacitidine to contribute to the future population PK and exposure response (safety/efficacy) analyses of pevonedistat.

5.1.3 Safety Objectives

The safety objective is to evaluate the safety of the combination of pevonedistat + venetoclax + azacitidine when compared with venetoclax + azacitidine in patients with AML who are unfit for induction therapy.

5.1.4 Exploratory Objectives

Exploratory objectives may be tested in a subset of patients and/or samples. The exploratory objectives may include but are not limited to the following:

- To evaluate the potential relationship between molecular characteristics of the tumor in terms of mutations, gene expression, protein abundance and protein/pathway activation status of apoptosis-related and Bcl-2 family-related effector genes/ proteins (eg, BCL2, NOXA BCL-XL, MCL1, BAX, BAK, and BH3) at baseline and efficacy and/or safety of the combination of pevonedistat +venetoclax + azacitidine versus venetoclax + azacitidine.
- To evaluate the impact of treatment on apoptosis and survival mechanisms at the RNA/protein levels within both bulk leukemia and leukemic stem/progenitor cells isolated from BMA or peripheral blood pre- and posttreatment in both treatment arms.
- To determine correlation of cytogenetic abnormalities/risk categories and molecular markers associated with poor prognosis in AML, such as FLT3 ITD, RUNX-1, IDH1, EZH2, ASXL1, TP53 with response and other clinical endpoints of interest in both treatment arms.
- To determine impact of therapy on elimination of leukemic stem cells in pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine.
- Identification of new somatic mutations posttreatment initiation and changes in activity of key signaling pathways in tumors from patients who initially respond to pevonedistat + venetoclax + azacitidine or venetoclax + azacitidine therapy and then exhibit progressive disease (PD).
- Confirm pevonedistat target transcriptional modulation of CRL protein substrates (NQO1, SLC7A11) in peripheral blood in pevonedistat + venetoclax + azacitidine arm.
- To compare minimal residual disease (MRD) negativity rates and depth with response, EFS, relapse-free survival (RFS), OS kinetics and duration of response between study arms.
- To compare MRD negativity rates and depths in patients who achieve CR or CRi in both treatment arms.
- Exploratory endpoints such as evaluating circulating serum proteins and miRNA signatures associated with response or resistance to pevonedistat + venetoclax + azacitidine treatment will be executed as warranted based on response, to support new emerging hypothesis or strategic need.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint of the study is EFS. EFS is defined as the time from study randomization to the date of failure to achieve CR/CRi (ie, discontinuing treatment without achieving CR/CRi), relapse from CR or CRi, or death from any cause, whichever occurs first [3].

5.2.2 Secondary Endpoints

5.2.2.1 Key Secondary Endpoint

The key secondary endpoint of the study is OS.

5.2.2.2 Other Secondary Endpoints

Other secondary endpoints are:

- 30- and 60-day mortality rates.
- Disease response rates:
  - CR rate.
  - CCR (CR + CRi) rate.
  - ORR (CR + CRi + PR) rate.
  - CR + CRh (CRh is defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts [platelets >50,000/μL and absolute neutrophil count (ANC) >500/μL]) rate.
  - Leukemia response rate (CR + CRi + PR + MLFS [marrow CR]).
- Duration of CR and CRi.
- Time to first CR, CRi, and PR.
- Pevonedistat plasma concentration-time data.

5.2.3 Safety Endpoints

The safety endpoints are:

- AEs, including SAEs.
- Clinical laboratory values.
- Electrocardiograms (ECGs).
- ECOG performance status.
- Vital signs.

5.2.4 Exploratory Endpoints

Exploratory endpoints may be tested in a subset of patients and/or samples. The exploratory endpoints may include but not limited to:

- Relative gene and protein expression levels of apoptosis-related and Bcl-2 family-related effectors such as BCL2, BCLXL, MCL1, BAX, and BAK in pre- and posttreatment samples of

both bulk leukemia and leukemic stem/progenitor cells isolated from BMA or peripheral blood in pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine arms.

- Screening cytogenetic abnormalities/risk categories and molecular markers associated with poor prognosis in AML such as FLT3 ITD, RUNX-1, IDH1, EZH2, ASXL1, TP53, K-RAS and correlation with clinical efficacy in both treatment arms.
- Clearance of leukemic stem cells in pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine.
- Evaluate potential mechanisms of treatment-emergent resistance, such as identification of new somatic mutations posttreatment initiation and changes in activity of key signaling pathways in tumors from patients who initially respond to pevonedistat + venetoclax + azacitidine or venetoclax + azacitidine therapy and then exhibit PD.
- Pevonedistat target transcriptional modulation of CRL protein substrates (NQO1, SLC7A11) in peripheral blood in pevonedistat + venetoclax + azacitidine arm.
- MRD negativity rates and depth in relation to response, EFS, RFS, OS kinetics and duration of response in both treatment arms.
- MRD negativity rates and depths in patients who achieve CR or CRi in both treatment arms.

6.0 STUDY DESIGN

6.1 Overview of Study Design

On the basis of the results from the phase 3 Study Pevonedistat-3001, the overall pevonedistat drug development program has been modified. These modifications also affect Study Pevonedistat-2002 and are captured in the current Protocol Amendment 4; these changes will become effective once Protocol Amendment 4 is implemented.

This study is a multicenter, randomized, open-label, controlled phase 2 study of the triple combination with pevonedistat, venetoclax, and azacitidine (investigational arm, Arm A) versus venetoclax plus azacitidine (control arm, Arm B) in adult patients with AML who are unfit for intensive chemotherapy.

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 L), 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. Following implementation of Protocol Amendment 4, the frequency of study assessments and clinic visits will be reduced as shown in the Modified SOE (Appendix A).

It is expected that approximately 150 patients will be enrolled in this study. At enrollment, patients will be randomized at a 1:1 ratio to receive (either pevonedistat + venetoclax + azacitidine [Arm A] or venetoclax + azacitidine [Arm B]) in 28-day treatment cycles. Patients will be stratified by age (18 to <75 years, ≥75 years) and AML subtype (de novo AML; secondary AML). Secondary AML

(sAML) is defined as AML after MDS or MPN, or therapy-related AML (t-AML) following cytotoxic therapy, and/or radiotherapy for a malignant or nonmalignant disease.

Investigational Arm (Arm A):

Triple Combination (Pevonedistat + Venetoclax + Azacitidine)

- Pevonedistat 20 mg/m^2 (IV via 60-minute infusion) on Days 1, 3, and 5.
- Venetoclax (400 mg) on Days 1 through 28 in Cycle 1.

  Ramp-up (Cycle 1 only): venetoclax will be administered at a dose of 100 mg on Day 1; 200 mg on Day 2; thereafter, at 400 mg on Days 3 through 28.

  Venetoclax (400 mg) on Days 1 through 28 of a 28-day cycle at Cycle 2 and beyond. If remission is confirmed in Cycle 1 or thereafter, Venetoclax (400 mg) can be administered on Days 1 through 21 of a 28-day cycle in subsequent cycles, to prevent potential prolonged myelosuppression and treatment delays. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles.
- Azacitidine 75 mg/m^2 (IV or SC) dosing on Days 1 through 7 **or** Days 1 through 5, 8, and 9.

Control Arm (Arm B):

Combination (Venetoclax + Azacitidine)

- Venetoclax (400 mg) on Days 1 through 28 in Cycle 1.

  Ramp-up (Cycle 1 only): venetoclax will be administered at a dose of 100 mg on Day 1; 200 mg on Day 2; thereafter, at 400 mg on Days 3 through 28.

  Venetoclax (400 mg) on Days 1 through 28 of a 28-day cycle at Cycle 2 and beyond. If remission is confirmed in Cycle 1 or thereafter, Venetoclax (400 mg) can be administered on Days 1 through 21 of a 28-day cycle in subsequent cycles, to prevent potential prolonged myelosuppression and treatment delays. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles.
- Azacitidine 75 mg/m^2 (IV or SC) dosing on Days 1 through 7 **or** Days 1 through 5, 8, and 9.

Dose reductions with the study drugs, delays, or changes in the schedule may be allowed if related to safety or other unavoidable circumstances as detailed in Section 8.3.

Patients, including those who achieve CR, may receive study treatment until they experience unacceptable toxicity, relapse, or PD as defined in this study (see Section 9.4.19 and Table 9.e). Patients 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 the patient is still

receiving clinical benefit from the treatment. The continuation of treatment will be based on the clinical judgment of the investigator and endorsed by the sponsor's project clinician (or designee). If the PD is a true progression of disease after CR/CRi, this would be scored as an event, despite the patient remaining on treatment. Patients who continue on study under these conditions must be reconsented before continuing study treatment. Patients may choose to discontinue treatment at any time.

Patients will attend the end-of-treatment (EOT) visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner. Patients will enter EFS follow-up (study visits every month to include physical examination, clinical blood tests, BMA sampling to be conducted every 3 months, or upon suspected relapse from CR or CRi). Patients will enter OS follow-up (contacted every 3 months to document subsequent therapies and survival status).

Disease response assessments will be based on the Revised Recommendations of the International Working Group (IWG) for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [1]. Formal disease assessments for study endpoints will be determined based on local BMA blast counts and transfusions, and central laboratory data. Disease response assessments will be carried out by the investigator.

Bone marrow samples (aspirate and biopsy [in accordance with institutional guidelines], see Appendix L, Table 1) will be collected at screening, during treatment, and during follow-up for blast count evaluation (to inform disease burden assessment). Bone marrow aspirates also will be used to analyze tumor cytogenetics, to analyze baseline somatic mutations and other molecular characteristics, to assess impact of therapy on depth and durability of response at predetermined time points using molecular techniques, and to identify treatment emergent mutations. Samples will be collected and analyzed from patients in both treatment arms. After implementation of Protocol Amendment 4, there will be no follow-up period and the collection of BMA samples will not be required, except as indicated per standard of care.

Sparse sampling for the determination of pevonedistat plasma concentrations will be collected from each patient in the investigational arm receiving pevonedistat + venetoclax + azacitidine (Arm A) to contribute to a population PK analysis of pevonedistat co-administered with venetoclax and azacitidine.

AEs and ECOG performance status will be assessed; ECGs, clinical laboratory values, and vital signs measurements will be obtained, to evaluate the safety and tolerability of the study drug treatments.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective 27 November 2017 [2]. Dose modification guidelines are presented in Section 8.3.

6.2 Number of Patients

Approximately 150 patients with AML will be enrolled in this study from approximately 85 study sites globally. Enrollment is defined as randomization of a patient into 1 of the study treatment arms, following the signing of the informed consent form (ICF).

6.3 Duration of Study

Patient enrollment into this study is complete. After implementation of Protocol Amendment 4, patients who remain on treatment will be assessed as indicated in the Modified SOE (Appendix A) until discontinuing treatment or they are transitioned off the study (see Section 9.11 for information on posttrial access). The total duration of the study is expected to be up to approximately 3 years.

Study treatments may continue as long as the patient derives clinical benefit or until 1 or more of the following criteria applies:

1. PD. Patients 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 the patient is still receiving clinical benefit from the treatment, based on the clinical judgment of the investigator, and the continuation is endorsed by the sponsor's project clinician (or designee).
2. Intercurrent illness that precludes further administration of study treatments.
3. Patient withdrawal of consent.
4. General or specific changes in patient condition that render the patient unable to receive further study treatments in the judgment of the investigator.
5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue study treatments.

6.3.1 Duration of an Individual Patient's Study Participation

Patients, including those who achieve CR, may receive study treatment until they experience unacceptable toxicity, relapse, or PD as defined in this study. Patients 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 the patient is still receiving clinical benefit from the treatment, based on the clinical judgment of the investigator, 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. Patients may choose to discontinue treatment at any time.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The study will be considered complete after the FA for EFS has been completed or the study has been terminated by the sponsor. The estimated time frame for study completion is approximately up to 3 years 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
Primary: EFS	Failure to achieve CR/CRi, relapse from CR/CRi, or death	Up to 3 years
Key Secondary: OS	The time from randomization to death from any cause	Up to 3 years
Other Secondary:		
• 30- and 60-day mortality rates	The proportion of patients who survive at most 30/60 days from the first dose of study drug(s).	
• Disease response rates: – CR rate – CCR (CR + CRi) rate – ORR (CR + CRi + PR) rate – CR + CRh rate – Leukemia response rate (CR + CRi + PR + MLFS [marrow CR])	As evaluated by the ~~i~~nvestigator	
• Duration of CR and CRi	CR and CRi: time to first documentation of PD.	
• Time to first CR, CRi, and PR	The time from randomization until the first CR, CRi, and PR.	
• Pevonedistat plasma concentration data	Pevonedistat concentration at prespecified collection time.	

AML: acute myeloid leukemia; CR: complete remission; CRh: <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/µL and absolute neutrophil count >500/µL); CRi: complete remission with incomplete blood count recovery; CCR: CR + CRi; EFS: event-free survival; MLFS: morphological leukemia-free state; ORR: overall response rate (CR + CRi + PR); OS: overall survival; PD: progressive disease; PR: partial remission.

6.3.4 Total Study Duration

It is anticipated that this study will last for up to approximately 3 years, after the first patient is enrolled.

6.3.5 Early Discontinuation of the Study

The study may be discontinued for reasons including medical or ethical reasons affecting the continued performance of the study, difficulties in the recruitment of patients, or due to sponsor decision.

Results of the registration-enabling Study Pevonedistat-3001 (PANTHER), 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, became available in September 2021. The primary endpoint of EFS was not met and no statistically significant benefits were observed with pevonedistat treatment. As such, Takeda will not pursue further development of pevonedistat in any indication.

Takeda is committed to continuing to provide study treatment to patients who are deriving benefit in Study Pevonedistat-2002 until they can be transitioned onto a PTA program (see Section 9.11) or discontinue for other protocol-specified reasons. Protocol Amendment 4 clarifies the overall study conduct and simplifies the assessments being performed, given the current state of the program and goal of decreasing the burden on patients.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be randomized to treatment:

1. Male or female patients aged ≥18 years.
2. Morphologically confirmed diagnosis of AML (World Health Organization [WHO] criteria 2008). Patients may have newly diagnosed primary de novo AML or sAML, defined as AML after MDS or MPN, or t-AML following cytotoxic therapy, and/or radiotherapy for a malignant or nonmalignant disease.
3. To qualify for this study, a patient must be considered to be unfit for treatment with a standard Ara-C and anthracycline induction regimen due to age or co-morbidities defined by 1 of the following:
   - ≥75 years of age.

   OR
   - ≥18 to <75 years of age with at least one of the following:
     - ECOG performance status of 2 or 3.
     - Severe cardiac disorder (eg, congestive heart failure requiring treatment, ejection fraction ≤50%, or chronic stable angina).
     - Severe pulmonary disorder (eg, carbon monoxide lung diffusion capacity ≤65% or forced expiratory volume in 1 second ≤65%).
     - CrCl <45 mL/min (but ≥30 mL/min as part of general eligibility criteria, see Inclusion # 4, Section 7.1).
     - Hepatic disorder with total bilirubin >1.5 times the ULN.
4. 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):

- Total bilirubin ≤1.5 times the ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll with direct bilirubin ≤3 times the ULN of the direct bilirubin. Elevated indirect bilirubin due to posttransfusion hemolysis is allowed.
- ALT and AST ≤3.0 times the ULN.
- CrCl ≥30 mL/min (calculated by the Modification of Diet in Renal Disease [MDRD] Study equation).
- Albumin >2.7 g/dL.

5. WBC count $<25 \times 10^9$/L. Patients who are cytoreduced with leukapheresis or with hydroxyurea may be enrolled if they meet the eligibility criteria before starting therapy.
6. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
7. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
8. Patient must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures, 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. History of MPN with BCR-ABL1 translocation or AML with BCR-ABL1 translocation.
2. Genetic diagnosis of acute promyelocytic leukemia.

3. Eligible for intensive chemotherapy and/or allogeneic stem cell transplantation.
4. Extramedullary AML without evidence of bone marrow involvement.
5. Prior treatment with hypomethylating agents for AML (hypomethylating agent treatment for prior MDS is not exclusionary).
6. Patients with either clinical evidence of or history of central nervous system involvement by AML.
7. Diagnosed or treated for another malignancy (except for adequately treated carcinoma in situ of any organ or nonmelanoma skin cancer) within 1 year before randomization or previously diagnosed with another malignancy and have any evidence of residual disease that may compromise the administration of pevonedistat, venetoclax or azacitidine. Prior MDS is also allowed, but the patient cannot have received treatment for MDS within 14 days before first dose of any study drug.
8. Psychological, social, or geographic factors that otherwise preclude the patient from giving informed consent, following the protocol, or potentially hamper compliance with study treatment and follow-up.
9. Patient has a WBC count $\geq 25 \times 10^9$/L.
10. Known hypersensitivity to pevonedistat, venetoclax, or azacitidine, and/or their respective excipients.
11. Female patients who intend to donate eggs (ova) during the course of this study or for 6 months after receiving their last dose of study drug(s).
12. Female patients who are both 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.
13. Male patients who intend to donate sperm or father a child during the course of this study or for 4 months after receiving their last dose of study drug(s).
14. Uncontrolled HIV infection.
    Note: Known HIV positive patients who meet the following criteria will be considered eligible:
    - CD4 count >350 cells/mm^3.
    - Undetectable viral load.
    - Maintained on modern therapeutic regimens utilizing non–CYP-interactive agents.
    - No history of AIDS-defining opportunistic infections.
15. Patient is known to be positive for hepatitis B or C infection, with the exception of those with an undetectable viral load within 3 months (hepatitis B or C testing is not required for eligibility assessment).

16. Known hepatic cirrhosis.
17. Treatment with strong CYP3A4 inducers within 14 days before the first dose of the study drug. Strong CYP3A4 inducers are not permitted during this study (see Appendix G).
18. Patients with the following will be excluded: uncontrolled intercurrent illness including, but not limited to known cardiopulmonary disease defined as unstable angina, congestive heart failure (New York Heart Association Class III or IV [Appendix H]), and/or ST elevation myocardial infarction within 6 months before first dose; severe symptomatic pulmonary hypertension requiring pharmacologic therapy; severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities; clinically significant arrhythmia (eg, well-controlled atrial fibrillation would not be an exclusion whereas uncontrolled atrial fibrillation would be an exclusion). Patients with medical comorbidities that will preclude safety evaluation of the investigational arm (pevonedistat + venetoclax + azacitidine [Arm A]) should not be enrolled.
19. Patient who has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, or cardiovascular disease that, in the medical judgement of the investigator, may compromise the delivery of pevonedistat, venetoclax, and/or azacitidine.
20. Patients with uncontrolled coagulopathy or bleeding disorder.
21. High blood pressure which cannot be controlled by standard treatments.
22. Prolonged rate QTc interval ≥500 msec, calculated according to institutional guidelines.
23. Left ventricular ejection fraction <40%, based on echocardiogram or multigated acquisition (MUGA) scan at screening (data to be available within last 3 months of screening).
24. As infection is a common feature of AML, patients with active infection are permitted to enroll provided that the infection is under control and no signs of systemic inflammatory response beyond low grade fever that makes patient clinically unstable in the opinion of the investigator. Patients with uncontrolled infection shall not be enrolled until infection is treated and brought under control.
25. Patients who have received an investigational agent (for any indication) within 5 half-lives of the agent and until toxicity from this has resolved to Grade 1 or less; if the half-life of the agent is unknown, patients must wait 4 weeks before receiving the first dose of study treatment.

8.0 STUDY DRUG

8.1 Study Drug Administration: Pevonedistat With Venetoclax and Azacitidine

All protocol-specific criteria for administration of all 3 study drugs 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 treatment cycle for the investigational triple combination (Arm A) is 28 days. The first dose of study drug must be administered within 5 days of randomization on study. The dosing and days specified for the triple treatment will occur as follows:

- Pevonedistat 20 mg/m^2 (via 60-minute IV infusion) on Days 1, 3, and 5.
- Venetoclax (400 mg) on Days 1 through 28 in Cycle 1.

  Ramp-up (Cycle 1 only): venetoclax will be administered at a dose of 100 mg on Day 1; 200 mg on Day 2; thereafter, at 400 mg on Days 3 through 28.

  Venetoclax (400 mg) will be administered on Days 1 through 28 of a 28-day cycle. If remission is confirmed in Cycle 1 or thereafter, venetoclax (400 mg) can be administered on Days 1 through 21 of a 28-day cycle in subsequent cycles, to prevent potential prolonged myelosuppression and treatment delays.

  If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles.
- Azacitidine (75 mg/m^2, IV or SC) on Days 1 through 7 **or** Days 1 through 5, 8, and 9.

Dosing of the drugs 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 of azacitidine should not be exceeded. If pevonedistat dosing is delayed, any remaining doses may only be administered on days when azacitidine is also given. If dosing is adjusted, study procedures should be performed on the actual day of dosing. In the investigational arm, azacitidine will be administered first followed by pevonedistat. Actual start and stop times of the study drug administration, should be recorded accurately.

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

8.2 Reference/Control Therapy: Venetoclax Plus Azacitidine

Venetoclax is a BCL-2 inhibitor that is used in combination with azacitidine for the treatment of newly diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Details regarding venetoclax, approved for patients with AML, are contained in the USPI [16]. The Summary of Product Characteristics (SmPC) for venetoclax in Europe is for CLL only [28]; all safety information for AML should be referenced to the USPI.

The treatment cycle for the combination control arm (Arm B) is also 28 days. During the ramp-up (Cycle 1 only), venetoclax will be administered at a dose of 100 mg on Day 1; 200 mg on Day 2, and at 400 mg on Days 3 through 28. Venetoclax (400 mg) will be administered on Days 1 through 28 (of a 28-day cycle) at Cycle 2 and beyond. If remission is confirmed in Cycle 1 or thereafter,

Venetoclax (400 mg) can be administered on Days 1 through 21 of a 28-day cycle in subsequent cycles, to prevent potential prolonged myelosuppression and treatment delays. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles. The tablets should be taken with a meal and water; they should not be chewed, crushed, or broken.

Azacitidine is a chemical analogue of cytidine that is widely used for the treatment of patients with AML and has been administered with pevonedistat in several clinical studies.

In a nonrandomized, open-label clinical study (NCT02203773 [16], 67 patients received the combination of venetoclax 400 mg (final dose after ramp-up) plus azacitidine 75 mg/m^2. At the time of analysis, for patients who achieved a CR, the median observed time in remission was 5.5 months (range, 0.4 to 30 months). The observed time in remission was the time from the start of CR to the time of data cutoff date or relapse from CR. Median time to first CR or CRh for patients treated with the combination was 1.0 month (range, 0.7 to 8.9 months).

Azacitidine 75 mg/m^2 (IV or SC) will be administered on Days 1 through 7 **or** Days 1 through 5, 8, and 9. Details regarding azacitidine are contained in the USPI and SmPC, respectively [29,30]. The amount of study drug (azacitidine) to be administered will be based on BSA. BSA will be calculated using a standard formula (see example in Appendix F) 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.

8.3 Dose Modification Guidelines

Toxicity will be evaluated according to the NCI CTCAE, version 5.0, 27 November 2017 [2].

8.3.1 Criteria for Retreatment and Dose Delays

8.3.1.1 Retreatment Within a Cycle

If dosing of any of the 3 study drugs 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 of azacitidine 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 venetoclax dosing is held for any reason, it may be resumed as soon as possible.

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 to ≤Grade 1 or to the patient's baseline values, the dose of study drug may be reduced (see Section 8.3.2) in the next cycle. This will apply to toxicity at least possibly related to protocol therapy. For toxicity not related to drug (eg, disease-related toxicity), although a similar dose reduction is permitted, in general it is discouraged. If the reduced dose is well tolerated and the toxicity leading to dose reduction was

≤Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the project clinician (or designee).

8.3.1.2 Initiation of a New Cycle

Treatment with study drugs will be repeated every 28 days. It is strongly recommended that dosing for the investigational arm (pevonedistat + venetoclax + azacitidine [Arm A]) and the control arm (venetoclax + azacitidine [Arm B]) 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, toxicity considered related to treatment with study drugs must have resolved to ≤Grade 1 or to the patient's baseline values.

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 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 project clinician (or designee). When deciding on dose modifications for management of myelosuppression, consider dose modification of venetoclax first before modifications of azacitidine. Pevonedistat is generally not associated with myelosuppression.

For toxicity not related to drug (eg, disease-related toxicity), a similar dose reduction is permitted but is generally discouraged. If the 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.

For hematologic toxicity, a delay in the initiation of a cycle by 4 weeks or greater because of lack of recovery from treatment-related hematologic toxicity (resolved to ≤Grade 1, to patient's baseline values, or to a level considered acceptable by the investigator) that is not related to leukemic infiltration will trigger a dose reduction if treatment resumes. If indicated, bone marrow evaluation will be performed to establish whether continued myelosuppression is related to persistent or progressing leukemic infiltration.

If criteria for resumption of therapy (described above) is not met, study treatments should be discontinued.

8.3.1.3 Venetoclax Dosing With CYP3A4 Inducers and Inhibitors

Moderate and strong CYP3A inducers and inhibitors are discouraged during venetoclax administration. If a patient requires use of CYP3A inducers, use with caution. However, in many instances, antifungal prophylaxis with "azole" therapy in neutropenic patients, CYP3A4 inhibitors may be required for management of infection in AML patients. Venetoclax should be administered at 200 mg (a 50% dose reduction from 400 mg) when given in the setting of moderate CYP3A inhibitors (ie, ciprofloxacin, diltiazem) and at 100 mg (75% dose reduction) in the setting of strong CYP3A inhibitors (ie, voriconazole), with the exception of coadministration with posaconazole where a dose reduction of venetoclax to 70 mg (83%) is required (refer to Table 7 in the USPI [16]).

The same dose reduction scheme is used if the patient is receiving venetoclax on Days 1 through 21 of the 28-day cycle in the setting of moderate and strong CYP3A inhibitors. Treatment with the reduced venetoclax dose should continue for the duration of coadministration. In the event the co-administered CYP3A inhibitor is discontinued, the venetoclax at 400 mg dose should be resumed 2 to 3 days after discontinuation of the inhibitor.

8.3.1.4 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 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 (as specified in Section 8.3.3.1) 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 <25,000/μL and following agreement by the sponsor's project clinician (or designee).

8.3.2.2 Venetoclax

Dose interruptions or modifications will be made for the following:

- Grade 4 hematologic toxicities only if investigator feels strongly that the cytopenias are related to venetoclax and not related to underlying disease or the use of other agents. Patients with baseline neutropenia or those who have significant bone marrow involvement may be particularly at high risk.
- If a patient achieves CRi or has a morphologically leukemia-free bone marrow after completing a cycle, venetoclax may be interrupted for up to 14 days after the last day of the cycle or until recovery of ANC >500/μL. Venetoclax may be resumed at the same dose level.
- If a patient presents with new onset Grade 4 neutropenia for more than 1 week during subsequent cycles, unless it is thought to be due to the underlying disease, venetoclax dosing may be interrupted until ANC recovery to >500/μL, in consultation with the sponsor's project clinician (or designee). Venetoclax may be re-initiated at a lower dose per discussion between the treating physician and the sponsor's project clinician (or designee).
- The dose levels for venetoclax dose adjustment are outlined in Table 8.a:

Table 8.a Dose Adjustments for Venetoclax

Current Dose of Venetoclax	Reduced Dose
400 mg	200 mg
200 mg	100 mg
100 mg	70 mg
70 mg	50 mg
50 mg	20 mg

Alternatively, the duration of venetoclax administration can be decreased (eg, decreased from 21-day to 14-day administration in Cycle 2 and beyond) rather than the dose being reduced, after discussion with the project clinician (or designee).

8.3.2.3 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 project clinician (or designee).

Cytopenias are common in the patient population studied in this trial. Dose modification for azacitidine for Grade 3 to 4 hematologic toxicities will be considered only if the treating physician strongly that the cytopenias were related to azacitidine and after appropriate dose reductions of venetoclax have been made as in Table 8.a.

If dose reductions of azacitidine are to be performed, guidelines are provided in Table 8.b.

Table 8.b Dose Reductions for Azacitidine

Current Dose of Azacitidine	Reduced Dose
75 mg/m^2	50 mg/m^2
50 mg/m^2	37.5 mg/m^2
37.5 mg/m^2	Hold azacitidine

Further reductions beyond what is shown in the table above or alternative reductions (eg, 75 mg/m^2 × 5 days) may be allowed if recommended by the investigator and after discussion with the project clinician (or designee).

- 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 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. When deciding on dose modifications for management of myelosuppression, consider dose modification of venetoclax first before modifications of azacitidine. Pevonedistat is generally not associated with myelosuppression.

8.3.3 Dose Modification for Nonhematologic Toxicities

8.3.3.1 Pevonedistat

Pevonedistat Dose Adjustment Based on Serum Transaminases and Total Bilirubin

It is anticipated that liver function tests (LFTs) (ie, 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 times the 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 times the 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 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) before first dosing, monitored during the study, 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/m2 to 10 mg/m2 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/m2 or 20 mg/m2 at the next cycle. For other Grade 3 to 4 nonhematologic toxicities at least possibly related to pevonedistat, pevonedistat will be held. If the toxicity returns to ≤Grade 1 or the patient's baseline status, pevonedistat may be re-started at 15 mg/m2 at the next cycle, and re-escalated to 20 mg/m2 at subsequent cycles at the discretion of the investigator as clinically indicated.

8.3.3.2 Venetoclax and Azacitidine

Although no dose adjustment is recommended in patients with mild or moderate hepatic impairment based on results of a population PK analysis, a trend for increased AEs was observed

in patients with moderate hepatic impairment; monitor these patients more closely for signs of toxicity during the initiation and dose ramp-up phase.

If Grade 3 or 4 nonhematologic toxicity is attributable to either agent (venetoclax or azacitidine), dose interruption of that agent is required. For patients who experience drug-related Grade 3 nonhematologic toxicity, venetoclax and/or azacitidine should be interrupted (determined by the attribution of the toxicity). The drug may be resumed when the patient has recovered to ≤Grade 1, and the dose must be reduced 1 dose level. If a patient has drug-related Grade 4 nonhematologic toxicity, the drug should be discontinued permanently. The dose of the agent can be decreased during a cycle, at the discretion of the treating physician, for chronic Grade 2 nonhematologic toxicity. Other dose modifications may be considered as clinically indicated with documentation and approval of the project clinician (or designee). The dose reduction guidelines for venetoclax and azacitidine nonhematologic toxicity are the same as those for hematologic toxicity, as outlined in Table 8.a and Table 8.b, respectively.

8.4 Excluded Concomitant Medications and Procedures

Table 8.c provides the list of medications and procedures that are prohibited during the study.

Management of potential venetoclax interactions with CYP3A and P-gp inhibitors for patients with AML is summarized in Table 8.d.

Table 8.c Excluded Concomitant Medications and Procedures

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	May be used judiciously but should not exceed a dose of 2 g in 24 hours for patients receiving pevonedistat.
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.
Clinically significant enzyme inducers (see Appendix G)	Excluded.
Strong CYP3A inhibitors	Refer to Table 8.d.
Moderate CYP3A inhibitors and P-gp inhibitors	Refer to Table 8.d.
P-gp substrates with narrow therapeutic index	Refer to Table 8.d.
Warfarin	An 18% to 28% increase in warfarin C_{max} and AUC of R- and S-warfarin is noted after single doses of venetoclax and warfarin. INR needs to be monitored closely.

Table 8.c Excluded Concomitant Medications and Procedures

Therapy	Comment/Exceptions
Known BCRP inhibitors (ie, cyclosporine)	For patients receiving pevonedistat, excluded, **but limited use is permitted only if clinically necessary and no suitable alternative exists.** The patient may receive the BCRP inhibitor from 24 hours after the last pevonedistat dose until 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the BCRP inhibitor may be administered from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle.
Any therapeutic agent other than pevonedistat	For example, androgens, supraphysiologic doses of corticosteroids (>10 mg/day prednisone or equivalent), erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate] are excluded.
Consumption of grapefruit or grapefruit juice	Patients should not consume food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before the first dose of study drug and throughout the study.

AUC: area under the plasma concentration-time curve; BCRP: breast cancer resistance protein; C_{max}: maximum observed plasma concentration; CYP: cytochrome P450; INR: international normalized ratio.

Table 8.d Management of Potential Venetoclax Interactions With CYP3A and P-gp Inhibitors for Patients With AML

Co-administered Drug	Initiation and Ramp-up Phase	Steady Daily Dose
Posaconazole	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 70 mg	Reduce venetoclax dose to 70 mg
Other strong CYP3A inhibitor (voriconazole)	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 100 mg	Reduce venetoclax dose to 100 mg
Moderate CYP3A inhibitor P-gp inhibitor	Reduce the venetoclax dose by at least 50%	

Source: Based on information in the venetoclax USPI [16].

AML: acute myeloid leukemia; CYP: cytochrome P450; P-gp: P-glycoprotein.

8.5 Permitted Concomitant Medications and Procedures

Concomitant medications will be documented in the patient's electronic medical record (electronic data capture [EDC]). Table 8.e lists concomitant medications and procedures permitted during the study.

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

Therapy	Comment
Anti-platelet agents (eg, aspirin, clopidogrel) and anticoagulants	May be used in patients who have controlled coagulopathy at baseline, as well as those who develop a coagulopathy on study. Note that patients with active uncontrolled coagulopathy are excluded from enrollment.
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 (MLFS), 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 $<0.5 \times 10^9$/L) with or without fever may receive G-CSF or GM-CSF between days 28 through 42 after discussion and agreement with the project clinician (or designee).
Platelet transfusion	Permitted as medically necessary per institutional guidelines (eg, for platelets $<10 \times 10^9$/L in the absence of clinical bleeding). Capture all transfusions in eCRF.
Red blood cell transfusion	To be considered for all patients with anemia, especially those with hemoglobin values ≤8 g/dL. Capture all transfusions in eCRF.

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

8.6 Precautions and Restrictions

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

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)

  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.

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

Patients should not receive live vaccines while receiving study medication in this protocol and for 2 weeks after completion of treatment, because of the possibility of receiving venetoclax.

8.7 Management of Clinical Events

8.7.1 Azacitidine

The most common adverse drug reactions for azacitidine are described in Section 4.7.3. Refer to the azacitidine USPI [29] or European Union (EU) SmPC [30], as applicable, for details regarding the management of clinical events attributed to azacitidine.

If unexplained reduction in serum bicarbonate levels to <20mEq/L occur, the dosage should be reduced by 50% on the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment course (see azacitidine USPI [29]).

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 Pevonedistat in Combination With Azacitidine

Common AEs reported for patients receiving the combination of pevonedistat and azacitidine in the clinical program are provided in Section 4.3. Also see the current IB.

For administering pevonedistat in combination with azacitidine, follow the guidance as appropriate in this protocol.

8.7.3 Venetoclax

Prophylaxis and Management of TLS

There is a potential for TLS with venetoclax-based therapies, especially in those with elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk for TLS, patients will receive tumor lysis prophylaxis, including hydration (eg, oral and/or IV) and treatment with an agent to reduce the uric acid level (eg, allopurinol, rasburicase) before and during the venetoclax ramp-up during cycle 1. For patients who had dose delay or interruptions, TLS prophylactic measures may need to be implemented based on the disease status before resuming treatment. TLS prophylaxis must be initiated in all such patients before the first venetoclax dose or first new escalated dose. See venetoclax USPI [16] or SmPC [28] for details.

During Cycle 1:

- All patients should have white blood cell count less than 25×10^9/L before initiation of venetoclax. Cytoreduction before treatment may be required.
- An oral agent to reduce the uric acid level (eg, allopurinol or substitute) must be initiated before first venetoclax dose. Patients allergic to or otherwise unable to receive allopurinol must use another uric acid reducer or rasburicase prior to venetoclax dosing.
- TLS chemistry tests (calcium, phosphorus, potassium, uric acid, and creatinine) predose on the first day of venetoclax and each day of a new dose before venetoclax dosing. TLS chemistry tests should also be checked between 4 to 12 hours after each new dose of venetoclax (ie, during the venetoclax ramp-up), and 24 hours after reaching final dose.
- TLS chemistry test results (ie, calcium, phosphorus, potassium, uric acid, and creatinine) must be reviewed by the investigator or treating physician in real time and before the patient's next dose to ensure appropriate patient management.
- If a patient meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax dose should be administered until resolution.
- For patients with risk factors for TLS (eg, circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment LDH levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose.

8.7.4 Guidance for Clinical Assessment and Management of Hemodynamic Compromise

It is essential that the patients receiving the combination of pevonedistat, venetoclax, 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, venetoclax, 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/h 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.

8.7.5 Management of Cytopenia and Infection

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

- If indicated, bone marrow evaluation will be performed to establish whether continued myelosuppression is related to persistent or progressing leukemic infiltration. When deciding on dose modifications for management of myelosuppression, consider dose modification of venetoclax first before modifications of azacitidine. Pevonedistat is generally not associated with myelosuppression.
- As general guidance for patients with, or who are expected to experience, significant protracted neutropenia (defined as ANC ≤500/uL for 7 days or with fever) are therefore at high risk of infection, prophylactic treatment with antibiotics (eg, fluoroquinolone, ciprofloxacin), antifungals (eg, voriconazole, fluconazole, parconazole), and antiviral agents (eg, acyclovir, entecavir or tenofovir) should be initiated, and continued at least through Cycle 1, per institutional guidance.
- Use of anti-infective prophylaxis should take into account possible DDI with study drugs (eg, CYP3A inhibitors) as described in Section 8.3.1 and in Table 8.d. Use of anti-infective agents are to be captured in eCRF.
- In general, the use of myeloid growth factors is discouraged and should be restricted. For patients in CR, CRi, or marrow CR (MLFS), growth factors may be used in specific

circumstances, per institutional guidelines and after discussion with the project clinician (or designee). Additionally, to avoid dose delays, patients who experience Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) with or without fever may receive G-CSF or GM-CSF between Days 28 through 42 after discussion and agreement with the project clinician (or designee).

8.7.6 Guidance Management of Leukostasis

Pevonedistat treatment should be withheld for patients who develop symptoms of leukostasis (see Section 8.3.2.1). Treatment may include leukapheresis and hydroxyurea administration, per institutional guidelines. When the WBC count is <25,000/μL and symptoms are improved, pevonedistat treatment may be restarted after consulting with the sponsor's project clinician (or designee). Treatment with azacitidine and venetoclax may continue as clinically indicated.

8.7.7 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) who are directly involved in the study conduct will be blinded to the treatment assignment of patients in the trial.

As of Protocol Amendment 4, Takeda's staff (or its designee) will be unblinded 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 Pevonedistat

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

Pevonedistat injection drug product formulation (as free base) consists of pevonedistat HCl in an aqueous solution of citric acid (anhydrous), trisodium citrate dihydrate, and ß-Cyclodextrin sulfobutyl ether at pH 3.3.

Each USP Type I glass vial of the compounded sterile solution is sealed with a Teflon-coated butyl rubber stopper and oversealed with an aluminum seal and a plastic cap.

Full details are available in the Pharmacy Manual.

8.9.2 Venetoclax

Venetoclax may be supplied by the site from commercial sources, depending on regional availability. Commercially available venetoclax is supplied as tablets for oral usage. Refer to the Study/Pharmacy Manual and the venetoclax USPI [16] or the EU SmPC [28], as applicable, for additional information regarding venetoclax.

8.9.3 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 Pharmacy Manual and the azacitidine USPI [29] or EU SmPC [30], as applicable, for additional information regarding azacitidine.

8.10 Preparation, Reconstitution, and Dispensing

Pevonedistat

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

The specified number of injection drug product vials should be removed and allowed to equilibrate to room temperature before dilution. The vial must not be shaken at any time during dose preparation. Before use, Pevonedistat Concentrate for Solution for Infusion vials should be brought to ambient conditions (15°C to 30°C [59°F to 86°F]) by removing the vials from the refrigerator and placing them at room temperature. Store in the original carton until time of use. 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 after removal from storage conditions of 2°C to 8°C (36°F to 46°F).

Using aseptic technique, the appropriate volume of drug should be withdrawn from vial(s), then injected into a 250 mL IV bag containing 5% dextrose solution or normal saline (0.9% sodium chloride) solution, and then gently inverted repeatedly to mix. The pevonedistat prepared IV bag must be used within 6 hours (time to the end of an injection) if stored at ambient temperature. Alternatively, the prepared IV bag is chemically stable and may be stored for up to 18 hours at 2°C to 8°C. After 18 hours of storage at 2°C to 8°C, the prepared IV bag must be used within 3 hours (time to the end of an injection) upon coming to ambient temperature.

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

Azacitidine

Refer to the azacitidine USPI [29] or the EU SmPC [30] for preparation and dispensing.

Venetoclax

Venetoclax is commercially available as a tablet for oral administration. Venetoclax may be sourced locally by the clinical sites when regulations allow for clinical site sourcing with appropriate drug labeling.

8.11 Packaging and Labeling

Pevonedistat

Pevonedistat (TAK-924/MLN4924) will be provided in 10 mL glass vials at a concentration of 10 mg/mL.

Venetoclax

Venetoclax is commercially available as a tablet for oral administration.

Azacitidine

Azacitidine is available as lyophilized powder in 100-mg, single-use vials from commercial supply. 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. Store in the original carton until time of use.

Details for the storage and handling of venetoclax are provided in the USPI [16] or the EU SmPC [28].

Details for the storage and handling of azacitidine are provided in the USPI [29] or the EU SmPC [30].

A drug dispensing log, including records of drug(s) received from the sponsor and drug(s) administered to the patients, will be provided. 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, GCP, applicable regulatory requirements, and 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. A full list of investigators is available in the sponsor's investigator database.

For 24-hour contact information, please refer to the Study Manual.

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 IRB/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 stratified by age (18 to <75 years, ≥75 years) and AML subtype (de novo AML; sAML). The first dose of study drugs must be administered 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

Following the implementation of Protocol Amendment 4 the frequency of study assessments and clinic visits will be reduced as shown in the Modified SOE (Appendix A).

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 institutional and local guidelines) in situations where a site visit cannot be conducted, such as in a coronavirus disease 2019 (COVID-19) pandemic. The reason for telemedicine (eg, COVID-19 related) and the assessments performed are to be captured in the EDC.

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.

9.4.2 Reconsent of Patients

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

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 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.

9.4.2.2 Reconsent of Patients after Implementation of Protocol Amendment 4

Patients may be allowed to continue study treatment (either treatment arm) after implementation of Protocol Amendment 4 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 after implementation of Protocol Amendment 4 must be reconsented before dosing on Day 1 of the next full treatment cycle and must follow the Modified SOE (Appendix A).

9.4.3 Patient Demographics

The date of birth (outside European Economic Area) or age (European Economic Area), race, ethnicity (optional depending on country), and sex of the patient are to be recorded during screening.

9.4.4 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.

9.4.5 Medical History

During screening, a complete medical history will be compiled for each patient. The history will emphasize the background and diagnosis of the patient's AML (see Section 7.1 Inclusion Criteria for the definition). Any history of prior hematologic disorder, such as myelodysplasia or other hematologic malignancies, should be documented as well as any treatments given for these disorders, including bone marrow transplantation, chemotherapy, hypomethylating agents, or other antineoplastic agents. Any prior history of chemotherapy or irradiation or bone marrow transplantation given for solid tumors also should be included as well as start and stop dates of each therapeutic agent and response to therapy. Medical conditions should also be documented, including, for example, cardiac disease (eg, cardiomyopathy, coronary artery disease, myocardial infarction, arrhythmias) as well as any medical condition that could impact the patient's clinical course and/or interfere with planned treatment or procedures in the protocol or be life-threatening.

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 specified times 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 azacitidine) to be administered will be based on BSA. BSA will be calculated using a standard formula (see example in Appendix F) 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 Modified Charlson Comorbidity Index Assessment

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

9.4.10 ECOG Performance Status

ECOG performance status will be assessed during screening and at the specified times. Refer to Appendix E for the ECOG performance status grading scale.

9.4.11 Vital Signs

Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected during screening and at the specified times and as clinically indicated. Vital sign measurements will be taken with the patient in the supine or sitting position.

9.4.12 ECG

A 12-lead ECG will be performed during screening and at the specified time points. Additional ECGs may be performed as clinically indicated. Echocardiogram or MUGA scan will be performed at screening if data for these is not available within 3 months of screening.

9.4.13 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 performed during screening.

9.4.14 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 (both treatment Arms A and B). Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

9.4.15 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. For additional details regarding excluded and permitted concomitant medications and procedures, see Section 8.4 and Section 8.5, respectively.

9.4.16 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.

9.4.17 Enrollment

Enrollment is achieved when the patient is randomized to 1 of the 2 study arms. Procedures for completion of the enrollment information are described in the IWRS and Study Manual.

9.4.18 Clinical Laboratory Evaluations

Following the implementation of Protocol Amendment 4, the clinical laboratory evaluations will be performed by a local laboratory and will no longer be performed at the central laboratory. Laboratory assessments will be carried out according to standard of care using local laboratory evaluations. Abnormal hematology and chemistry data will be collected and recorded in the eCRF only to the extent that they are needed to document or support an AE. Laboratory assessments to inform dosing decisions and routinely monitor patients do not need to be recorded in the eCRF.

Local laboratory evaluations may be done more frequently at the investigator's discretion, for instance management of anemia.

BMA testing for the diagnosis and eligibility criteria will be determined per local laboratory results. Sites will provide local cytogenetic and mutation reports, as allowed per local regulations.

9.4.18.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of clinical hematology parameters and serum chemistry and TLS panels are shown in Table 9.a and Table 9.b, respectively. Select serum chemistry panel is shown in Table 9.c. Urine samples for analysis of the parameters shown in Table 9.d will be obtained at specified times.

Table 9.a 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 J.
Platelet (count)

ANC: absolute neutrophil count.

Table 9.b Complete Serum Chemistry and Tumor Lysis Syndrome Panels

Complete Serum Chemistry Panel	
Albumin	CO_2
ALP	Chloride
ALT	Creatinine
AST	Glucose
Bilirubin (direct)	LDH
Bilirubin (total)	Magnesium
Blood uric acid	Phosphate
BUN	Potassium
Calcium	Sodium
TLS Panel	
Blood uric acid	
Calcium	
Creatinine	
Phosphate	
Potassium	

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CO_2: carbon dioxide; LDH: lactate dehydrogenase; TLS: tumor lysis syndrome.

Table 9.c Select Serum Chemistry Panel

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

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

Coagulation testing (prothrombin time and activated partial thromboplastin time [aPTT]) will be done at screening and at specified times.

Blood samples for analysis of reticulocyte counts and ferritin levels will be obtained at specified times.

Table 9.d Urinalysis With Microscopic Analysis

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

Urinalysis assessments will be performed as in Table 9.d. These samples will be analyzed by a local laboratory.

Creatinine clearance will be estimated using the MDRD Study equation (Appendix K).

9.4.19 Disease Assessment

Formal disease assessments for study endpoints will be determined based on local BMA blast counts (blast counts from the bone biopsy may be used in the event the aspirate sample is inadequate and a biopsy was done) and clinical laboratory evaluations (performed at a local laboratory). The investigator's assessment of disease will be entered in the eCRF for each time point. The blast percentage should be correlated with an estimate of the blast count from the marrow biopsy section.

Patients who receive myeloid growth factors will not be included in assessment of neutrophil response within 2 weeks of growth factor administration.

Assessments of disease response (see Table 9.e) are based on the criteria outlined in the European Leukemia Net 2017 guidelines [3].

Table 9.e Response Criteria

Category	Definition	Comment
Response		
CR_{MRD-}	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC.	Sensitivities vary by marker tested, and by method used; therefore, the test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics).
CR	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC $\geq 1.0 \times 10^9$/L (1000/μL); platelet count $\geq 100 \times 10^9$/L (100,000/μL).	MRD^+ or unknown.
CRi	All CR criteria except for residual neutropenia ($<1.0 \times 10^9$/L [1000/μL]) or thrombocytopenia ($<100 \times 10^9$/L [100,000/μL]).	
CRh	A response of CRh is defined as bone marrow with <5% blasts, peripheral blood neutrophil count $>0.5 \times 10^3$/μL and peripheral blood platelet count $>0.5 \times 10^5$/μL.	
MLFS	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required.	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated, or cellularity should be at least 10%.
PR	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%.	Especially important in the context of phase 1-2 clinical trials.
Treatment failure		
Primary refractory disease	No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause.	Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of 7 + 3; the likelihood of responding to such regimens is lower after failure of a first.
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia.	
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available.	

Table 9.e Response Criteria

Category	Definition	Comment
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CRi, PR, MLFS; and criteria for PD not met.	Period of stable disease should last at least 3 months.
Progressive disease	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15 percentage point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/μL], and/or platelet count to >50 × 10^9/L [50,000/μL] nontransfused); or • >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (>25,000/μL) (in the absence of differentiation syndrome); or • New extramedullary disease.	Category mainly applies for older patient given low-intensity or single-agent "targeted therapies" in clinical trials. In general, at least 2 cycles of a novel agent should be administered. Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 weeks apart; the date of progression should then be defined as of the first observation date. Some protocols may allow transient addition of hydroxyurea to lower blast counts. "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms.
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, or CRi)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease.	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC.	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics).

Source: ELN 2017 guidelines [3].

AML: acute myelogenous leukemia; ANC: absolute neutrophil count, CR: complete remission; CRh: complete remission with partial hematologic recovery; CRi: complete remission with incomplete hematologic recovery; CR_{MRD-}: CR without measurable residual disease; MFC: multiparameter flow cytometry; MLFS: morphologic leukemia-free state; MRD: measurable residual disease; PR: partial remission; RT-qPCR: real-time quantitative polymerase chain reaction; WBC: white blood cell.

9.4.20 Biomarker, Pharmacodynamic, and PK Samples

Details regarding the preparation, handling, and shipping of samples are provided in the central laboratory manual (Collection Flow Chart).

9.4.20.1 Primary Specimen Collection

Primary specimen collections are summarized in Table 9.f. See Table 9.f footnote for specific changes in specimen collection following implementation of Protocol Amendment 4.

Table 9.f Specimen Name in the Schedule of Procedures

No.	Specimen Name in the Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
1	Locally generated pathology report	N/A	N/A	N/A	Cytogenetics abnormalities determination	Mandatory
2	Locally generated cytogenetic report	N/A	N/A	N/A	Cytogenetics abnormalities determination	Mandatory
3	Locally generated mutational report	N/A	N/A	N/A	Genetic abnormalities determination	Mandatory
4	Fresh BMA sample for molecular analysis (MOA and LSCs enumeration)	Fresh bone marrow	Fresh cells for flow	N/A	Biomarker measurements in fresh BMA	Mandatory
5	Fresh BMA sample for molecular analysis, MRD, and cytogenetic risk category	Fresh bone marrow	Fresh cell	DNA RNA	Biomarker measurements in fresh BMA	Mandatory
6	Plasma samples for circulating biomarkers	Plasma	N/A	N/A	Biomarker measurements in plasma	Mandatory
7	Blood samples for MOA and LSCs enumeration	Peripheral blood	N/A	N/A	Biomarker measurements in blood	Mandatory
8	Blood samples for RNA	Peripheral blood	RNA	N/A	Biomarker measurements in blood	Mandatory
9	Serum samples for circulating biomarkers	Serum	N/A	N/A	Biomarker measurements in serum	Mandatory
10	Plasma samples for pevonedistat PK	Plasma	N/A	N/A	PK measurements	Mandatory

BMA: bone marrow aspirate; LSC: leukemic stem cell; MRD: measurable residual disease; MOA: mechanism of action; N/A: not applicable; PK: pharmacokinetics.

Collection of peripheral blood samples for exploratory analyses (MOA and LSC enumeration), plasma samples for circulating biomarkers, serum samples for circulating biomarkers, plasma samples for PK will be discontinued once Protocol Amendment 4 is implemented. Collection of bone marrow aspirates will be reduced (see Modified Schedule of Events [Appendix A]).

9.4.20.1.1 Locally Generated Reports Collection

Locally generated reports will be submitted to sponsor when allowed per local regulations. The bone marrow pathology and cytogenetics reports from the local laboratories will be submitted to the sponsor for recording of cytogenetic abnormalities and risk categories determination per ELN [3] at screening and at every subsequent visit when available.

Screening mutation reports from the local laboratories will be submitted to the sponsor for recording.

9.4.20.1.2 Fresh Bone Marrow Aspirate Sample Collection for Molecular Analysis

Fresh bone marrow aspirate samples will be collected. Two separate tubes will be collected and shipped to specialty laboratories for molecular characterization to:

- Identify biomarkers that are predictive of efficacy and/or safety of the combination of pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine. A portion of the bone marrow aspirate sample obtained at screening will be sent to specialty laboratories for baseline molecular characterization of the patient's tumor (analyses may include next-generation sequencing [NGS], RNAseq, gene expression, protein abundance and protein/pathway activation status of apoptosis-related and Bcl-2 family-related effector genes/ proteins, cytogenetic abnormalities and molecular markers associated with poor prognosis in AML).
- Determine changes in apoptosis and survival mechanisms within both bulk leukemia and leukemic stem/progenitor cells isolated pre- and posttreatment in both treatment arms.
- Determine impact of therapy on elimination of leukemic stem cells in pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine arms.
- Determine depth and durability of response (MRD) over time and compare with response and kinetics of response in both treatment arms. Analysis will be done for disease burden before and following treatment using either flow cytometry, NGS, or proteomic based approaches.
- Evaluate mechanisms of treatment-emergent resistance. Bone marrow aspirates obtained at relapse from patients who initially respond to pevonedistat + venetoclax + azacitidine or venetoclax + azacitidine therapies and then exhibit PD, will be evaluated for potential mechanisms of treatment-emergent resistance, such as new somatic mutations and key signaling pathways, or change in pathway activity.

9.4.20.1.3 Blood Sample Collection for RNA, Mechanism of Action, and Leukemic Stem Cells Enumeration

Blood samples will be collected and may be sent to a specialty laboratory for molecular characterization to:

- Confirm pevonedistat target transcriptional modulation of CRL protein substrates (NQO1, SLC7A11) in the pevonedistat + venetoclax + azacitidine arm.
- Determine impact of therapy on elimination of leukemic stem cells in pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine arms in peripheral blood.
- Determine changes in apoptosis and survival mechanisms within both bulk leukemia and leukemic stem/progenitor cells isolated pre- and posttreatment from peripheral blood in both treatment arms.

- Determine protein abundance and protein/pathway activation status of apoptosis-related and Bcl-2 family-related effector genes/proteins in tumor cells isolated from peripheral blood at screening and correlate with response.

9.4.20.1.4 Serum and Plasma Samples Collection for Circulating Biomarkers

Serum and plasma samples will be collected to evaluate circulating serum and plasma proteins and miRNA signatures associated with response or resistance to pevonedistat + venetoclax + azacitidine treatment.

9.4.21 PK Measurements

Following the implementation of Protocol Amendment 4, blood samples for PK analysis will not be collected (see Modified SOE [Appendix A]).

Blood samples for the determination of pevonedistat (and its metabolites, if appropriate) plasma concentrations will be collected from all patients from the pevonedistat + venetoclax + azacitidine. 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 amount of blood samples, preparation, handling, and shipping of samples are provided in the central laboratory (Collection Flow Chart).

9.4.22 Pharmacodynamic Measurements

All of the pharmacodynamic measurements to be done are exploratory and retrospective in nature and are as follows:

- Baseline molecular characterization of the patient's bone marrow and peripheral blood will allow the identification of subgroups (beyond demographics and clinical features) that can be correlated with response or resistance to the combination of pevonedistat + venetoclax + azacitidine. For example, these subgroups may be based on patients' baseline abundance and activation status of Bcl-2 family effector proteins, such as: BCL2, NOXA BCL-XL, MCL1, BAX, BAK, and BH3 as well as subgroups based on AML biology, such as: cytogenetic profile and/or somatic mutations. In addition, comparing baseline with posttreatment molecular characterization of the patient's bone marrow and peripheral blood will allow evaluation of the mechanism of action (MOA) of the triple combination; to confirm pevonedistat-induced target modulation of CRL protein substrates, such as NQO1 and SLC7A11, as well as to determine whether the survival signaling within cells is skewed toward one antiapoptotic BCL2 family member or another at baseline, whether there are differences in

modulation between the treatment arms and the general impact of adding pevonedistat to venetoclax + azacitidine.

- In this study, identification of somatic mutations at screening in both treatment arms using next-generation sequencing and correlation with clinical efficacy and safety will be performed. In addition, relationship with molecular markers associated with poor prognosis in AML, such as FLT3 ITD, RUNX-1, EZH2, ASXL1, N-RAS, K-RAS, and TP53, in both treatment arms and correlation with clinical efficacy will be determined. Mutational data, such as FLT3 ITD, IDH1, and IDH2 are increasingly being used as a complementary tool to influence the selection of the most appropriate therapy in AML. Importantly, initial data form the phase1b Study C15009 single arm study of evaluating pevonedistat + azacitidine in elderly patients with AML shows notable activity of the combination in the hard-to-treat TP53 mutant patient population. Finally, the targeted DNA sequencing of BMA collected at screening in the Study C15009, was conducted to identify molecular subgroups correlated with clinical outcome. Based on this analysis, a decision tree model was developed to classify patients who respond to pevonedistat + azacitidine. This algorithm is being evaluated for its predictive and/or prognostic performance in the phase 2 study, Pevonedistat-2001. Similarly, the potential of the described algorithm to predict response to the triple combination of pevonedistat + venetoclax + azacitidine will be evaluated in this study.
- Leukemic cells that remain in the bone marrow following treatment are a major cause of disease relapse. 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 1) could improve prognostication by identifying submicroscopic disease during remission [31]. Measurement of MRD is receiving recognition as a potential tool to assess the quality of response after chemotherapy and to plan postremission strategies. In this study, BMAs collected at screening and specified time points during treatment and/or at relapse will be used to evaluate and compare depth and duration of response between both treatment arms by following parameters such as residual tumor cells, residual mutation load, and emergent of new clones. BMAs obtained at relapse will be evaluated for potential mechanisms of treatment-emergent resistance. In addition, the hypothesis that high leukemic stem cells frequency at baseline predicts high MRD and poor survival [32] as well as the impact of therapy on elimination of leukemic stem cells in both treatment arms will be tested.

9.5 Completion of Study Treatment (for Individual Patients)

A patient will be considered to have completed study treatment once the patient enters posttreatment follow-up.

9.6 Completion of Study (for Individual Patients)

A patient will also be considered to have completed the study if discontinued from study drug treatment (refer to Section 9.7) and 1 or more of the following situations occur:

- Death.
- Consent withdrawal.
- Investigator decision.
- Study terminated by the sponsor.
- Lost to follow-up.
- Transfer of patient to the PTA program.

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

Once the study has been completed, all study procedures outlined for the end of treatment visit will be completed as specified in the Modified SOE (Appendix A). After study completion, no new information will be collected from the completed patient and added to the existing data or any database.

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Study drug(s) must be permanently discontinued for patients meeting any of the following criteria:

- Study drug–related toxicity causing a study drug hold of >6 weeks.
- Unacceptable toxicity.
- PD.

  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 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 patient.
- 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 Modified SOE (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF, along with any other details. Patients who are randomized to a treatment arm but do not receive study drug for any reason will not be replaced.

In the case of study termination by the sponsor, eligible patients may have continued access to pevonedistat as described in Section 9.11.

9.8 Withdrawal of Patients From Study

The investigator also has the right to withdraw patients from the study treatment for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient.
- Death.
- Transfer of patient to the PTA program.
- 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, Response, and OS)

The Modified SOE (Appendix A) will be followed after implementation of Protocol Amendment 4. Long-term follow up visits (EFS/response and OS) will no longer be required; patients will complete an End of Treatment visit 30 (+10) days after the last dose of study drug(s) or before the start of antineoplastic therapy if that occurs sooner.

9.11 Posttrial Access

Where permitted by local regulations, and if the responsible investigator and the sponsor agree that the patient would derive benefit from or would be harmed without continued access to the assigned treatment regimen, patients may continue to receive access to the assigned treatment regimen after the study is completed. If a posttrial access (PTA) program should become an option for a patient, then pevonedistat + venetoclax + azacitidine or venetoclax + azacitidine, depending on treatment arm assignment, may be provided through the PTA program.

9.12 Duration of PTA

If a PTA program should become an option for a patient, as described in Section 9.11, the sponsor may continue to provide the assigned treatment regimen to that patient through the PTA program. Continued access to the assigned treatment regimen 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); if the benefit-risk no longer favors the individual, an appropriate alternative therapy becomes available, or the comparators, eg, venetoclax, become available either commercially or via another access mechanism. PTA may be terminated in a country or geographic region upon decision by the sponsor or where pevonedistat, venetoclax, or azacitidine 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 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 administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

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

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 [2]. 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 white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

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

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

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

All SAEs 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 study drug are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study; 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.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 [2]. 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.
  - 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 Global Pharmacovigilance Department or designee from the time of the signing of the ICF up to first dose of study drug and will also be recorded in the eCRF.
  - Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance Department (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 Global Pharmacovigilance Department (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 sending a completed pregnancy form to the Takeda Global Pharmacovigilance Department or designee. The pregnancy must be followed for the final pregnancy outcome.

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

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

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

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

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

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

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

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Takeda Safety Monitoring

Safety data will be reviewed and assessed routinely by a Global Pharmacovigilance Safety Team and a Safety Management Committee throughout the conduct of the study. These reviews will include a Global Safety Lead from the study team, as well as other representation from the Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, and Clinical Operations departments at Takeda. An initial safety assessment will be performed after 10 patients have completed at least 1 cycle of treatment.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

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

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

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

12.2 Record Retention

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

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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 2-sided 90% and 95% CIs for time-to-event data.

A statistical analysis plan (SAP) will be prepared. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final CSR.

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 any of the study medications (pevonedistat, venetoclax, or azacitidine). Patients will be analyzed according to the actual treatment they receive. Patients who receive any dose of pevonedistat will be included in the pevonedistat + venetoclax + azacitidine arm (Arm A), and patients who did not receive any dose of pevonedistat and receive at least 1 dose of venetoclax + azacitidine will be included in the venetoclax + azacitidine arm (Arm B), 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 do not have major protocol deviations, as determined by the study clinician.
- **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 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 the ITT population. The analysis of other secondary efficacy endpoints will be performed on the ITT population, unless specified otherwise.

13.1.3.1 Analyses for Primary Efficacy Endpoint

The primary endpoint of the study is EFS. The analysis of EFS will use the investigator-assessment. EFS is defined as the time from study randomization to the date of failure to achieve CR or CRi, relapse from CR/CRi, or death from any cause, whichever occurs first. For patients who have achieved CR/CRi, if the relapse is not observed by the time of the analysis, patients will be censored at the date of last disease assessment. If patients fail to achieve CR or CRi, the date of treatment failure will be set on the day of randomization.

Detailed rules of handling missing assessments and censoring for the analysis of EFS will be described in the SAP. The stratified log-rank test statistic will be used to compare the treatment groups with respect to EFS at the 1-sided $\alpha = 5\%$ significance level. A stratified unadjusted Cox model will be used to estimate the HR and its 2-sided 90% CIs for the treatment effect. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 90% CIs, will also be provided for each treatment group. Two-sided 95% CIs for HR and median EFS will also be computed.

13.1.3.2 Analyses of Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is OS, which is defined as time from randomization to death from any cause. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

The 1-sided log-rank test at the $\alpha = 5\%$ significance level will be used to compare the treatment groups with respect to OS and calculate the p-value. In addition, a stratified unadjusted Cox model will be used to estimate the HR and its 2-sided 90% CIs for the treatment effect. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 90% CIs, will also be provided for each treatment group. Two-sided 95% CIs for HR and median OS will also be computed. Additional sensitivity analyses for OS may be also conducted as appropriate.

13.1.3.3 Analyses of Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints are: 30- and 60-day mortality rates; disease response rates: CR rate, CCR (CR + CRi) rate, ORR (CR + CRi + PR) rate, CR + CRh rate, leukemia response rate (CR + CRi + PR + MLFS[mCR]); duration of CR and CRi; time to first CR, CRi, and PR.

Patients who receive myeloid growth factors will not be included in assessment of neutrophil response within 2 weeks of growth factor administration.

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

30- and 60-Day Mortality Rates

The 30- and 60-day mortality rates are defined as the proportion of patients who survive at most 30 and 60 days, respectively, from the first dose of study drug, which will be summarized by treatment arm in a table. The relative risk with its 2-sided 90% and 95% CIs will be calculated. The absolute rate difference will also be provided with its 90% and 95% CIs calculated using the asymptotic method.

Disease Response Rates: CR Rate, CCR (CR + CRi) Rate, ORR (CR + CRi + PR) Rate, CR + CRh Rate, Leukemia Response Rate (CR + CRi + PR + MLFS[mCR])

The disease response rates are defined as the proportion of patients who achieve the corresponding response in the corresponding group of patients. The number and percentage of patients for each definition of response will be summarized by treatment group. The relative risk with its 2-sided 90% and 95% CIs will be calculated. The absolute rate difference will also be provided with its 90% and 95% CIs calculated using the asymptotic method.

The key analysis will be based on the ITT population, with response non-evaluable patients treated as nonresponders. Sensitivity analysis will be performed using the response-evaluable population.

Duration of CR and CRi

Duration of CR and CRi will be summarized descriptively using the K-M method based on the responders.

Time to First CR, CRi, and PR

Time to first CR, CRi, and PR is defined as time from randomization to the first documented CR or CRi or PR, whichever occurs first. The analysis will be performed using the K-M estimate, with the presentation of medians and associated 90% and 95% confidence intervals.

13.1.4 PK Analysis

13.1.4.1 PK Noncompartmental Analysis

PK parameters will be summarized using descriptive statistics. Individual pevonedistat concentration-time data and individual PK parameters will be presented in listings and also tabulated using summary statistics.

13.1.4.2 PK Sampling Intended for Population PK Analysis

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

13.1.5 Pharmacodynamic Analysis

Baseline cytogenetics data, mutation status, and apoptosis-related and Bcl-2 family-related effector genes/proteins status may be summarized descriptively by treatment arm and correlated with best response and other endpoints of interest in the subset of patients where the data are available.

Further changes in sample collection and/or exploratory analyses may be implemented based on emerging scientific knowledge. Results of available exploratory biomarkers may be reported outside of the CSR and/or added as an addendum to the CSR.

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 performance score, ECG results, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

All AEs will be coded using the MedDRA. 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 System Organ Class, High-Level Term, and Preferred Term (PT), and will include the following categories:

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

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

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

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

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

All concomitant medications collected from screening through the study period will be classified to PT according to the WHO Drug Dictionary. All blood (RBC, platelet) transfusions will also be reviewed to determine transfusion dependence or independence.

The 30- and 60-day mortality rates are defined as the proportion of patients who survive at most 30 and 60 days, respectively, 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.

13.2 IA and Event Size Re-estimation

One IA and one FA for statistical analyses of efficacy were initially planned; however, following decisions and changes made within the pevonedistat program after read-out from Study Pevonedistat-3001, the IA has been removed from Study Pevonesdistat-2002 and no event size re-estimation will be conducted. Only FA will be conducted, the timing of which will no longer be based on EFS events but instead it will be based on sponsor discretion. An updated analysis for safety data is planned at study closure. Upon implementation of Protocol Amendment 4, the frequency of study assessments and clinic visits will be reduced as shown in the Modified SOE (Appendix A).

13.3 Determination of Sample Size

The study was originally designed to have approximately 85 EFS events to provide 80% power to detect a HR of 0.58 (median EFS of 19 months in the investigational pevonedistat + venetoclax + azacitidine arm [Arm A] versus 11 months in the venetoclax + azacitidine control arm [Arm B], assuming exponential distribution of EFS) using a stratified log-rank test at 1-sided 5% significance level.

Given the changes being made in the pevonedistat program as noted in Section 13.2, FA for EFS will be conducted after Protocol Amendment 4 is implemented using the number of EFS events observed at FA.

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 including, but not limited to, the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient 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 patients. 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 patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of the primary study assessment.

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

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

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, 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 designee).

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

15.2 Patient Information, Informed Consent, and Patient 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, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. 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 patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

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

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

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient'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 patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, EMA, UK MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient'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 patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

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 patient in the study must be insured in accordance with the regulations applicable to the site where the patient 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 patients. Refer to the clinical study site agreement regarding the sponsor's policy on patient 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. 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.
2. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. November 2017.
3. 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.
4. DiNardo CD, Pratz KW, Letai A, Jonas BA, Wei AH, Thirman M, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol 2018;19(2):216-28.
5. Liu Y, Hu M. Testing multiple primary endpoints in clinical trials with sample size adaptation. Pharmaceutical Statistics 2016;15(1):37-45.
6. Dohner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. New England Journal of Medicine 2015;373(12):1136-52.
7. Burnett AK, Hills RK, Hunter AE, Milligan D, Kell WJ, Wheatley K, et al. The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: results from the LRF AML14 and NCRI AML16 pick-a-winner comparison. Leukemia 2013;27(1):75-81.
8. Pollyea DA, DiNardo C, Thirman M, Letai A, Wei AH, Jonas BA, et al. Results of a phase 1b study of venetoclax plus decitabine or azacitidine in untreated acute myeloid leukemia patients ⩾ 65 years ineligible for standard induction therapy. J Clin Oncol 2016;34(15_suppl). 7009.
9. Wei AH, Strickland SA, Roboz GJ, Hou J, Fiedler W, Lin T, et al. Safety and Efficacy of VenetoclaxPlus Low-Dose Cytarabinein Treatment-Naïve Patients Aged ⩾65 Years With Acute Myeloid Leukemia. Blood 2016;128(22). 102.
10. Stone R, Mandrekar S, Sanford B, Laumann K, Geyer S, Bloomfield C, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. New England Journal of Medicine 2017;377:454-64.
11. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood 2017;130(6):722-31.
12. Knorr KL, Schneider PA, Meng XW, Dai H, Smith BD, Hess AD, et al. MLN4924 induces Noxa upregulation in acute myelogenous leukemia and synergizes with Bcl-2 inhibitors. Cell Death Differ 2015;22(12):2133-42.

13. Konopleva M, Pollyea DA, Potluri J, Chyla B, Busman T, McKeegan E, et al. A Phase 2 Study of ABT-199 (GDC-0199) in Patients with Acute Myelogenous Leukemia (AML). Blood 2014;124(21). 118.
14. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2016;374(4):311-22.
15. Konopleva M, Pollyea DA, Potluri J, Chyla B, Hogdal L, Busman T, et al. Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia. Cancer Discov 2016;6(10):1106-17.
16. Venclexta (venetoclax tablets). Prescribing Information. North Chicago, IL, US: AbbVie Inc., Revised 5/2019.
17. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019;133(1):7-17.
18. Souers AJ, Leverson JD, Boghaert ER, Ackler SL, Catron ND, Chen J, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nature Medicine 2013;19(2):202-8.
19. 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.
20. 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.
21. Lancet JE, Uy GL, Cortes J, Newell LF, Lin TL, Ritchie E, et al. Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. Journal of Clinical Oncology 2016;34(no. 15_suppl). 7000.
22. Bose P, Gandhi V, Konopleva M. Pathways and mechanisms of venetoclax resistance. Leuk Lymphoma 2017;58(9):1-17.
23. 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(7239):732-6.
24. Soucy TA, Smith PG, Rolfe M. Targeting NEDD8-activated cullin-RING ligases for the treatment of cancer. Clin Cancer Res 2009;15(12):3912-6.
25. Swords RT, Kelly KR, Smith PG, Garnsey JJ, Mahalingam D, Medina E, et al. Inhibition of NEDD8-activating enzyme: a novel approach for the treatment of acute myeloid leukemia. Blood 2010;115(18):3796-800.
26. Visconte V, Nawrocki ST, Espitia CM, Kelly KR, Possemato A, Beausoleil SA, et al. Comprehensive quantitative proteomic profiling of the pharmacodynamic changes induced by

MLN4924 in acute myeloid leukemia cells establishes rationale for its combination with azacitidine. Leukemia 2016;30(5):1190-4.

27. 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 Leukemia and Myelodysplastic Syndromes: A Phase 1 study. Br J Haematol 2015 (in press).
28. Venclyxto (venetoclax). Summary of Product Characteristics. Maidenhead, UK: AbbVie Ltd, Revised 8 April 2020.
29. Vidaza (azacitidine for injection). Prescribing Information. Summit, NJ, USA: Celgene Corporation, Revised 03/2020.
30. Vidaza (azacitidine). Summary of Product Characteristics. Utrecht, Netherlands: Celgene Europe B. V., Revised 02 Apr 2019.
31. 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.
32. van Rhenen A, Feller N, Kelder A, Westra AH, Rombouts E, Zweegman S, et al. High stem cell frequency in acute myeloid leukemia at diagnosis predicts high minimal residual disease and poor survival. Clin Cancer Res 2005;11(18):6520-7.
33. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics 1999;55(3):853-7.
34. 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.
35. 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.
36. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.
37. 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.
38. 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 Modified Schedule of Events

Upon implementation of Protocol Amendment 4, this modified SOE will be followed for patients continuing on the study. The original (Protocol Amendment 2) SOE has been moved to Appendix L for reference purposes.

	Treatment Cycle (28 Days) [a, b]				
	Day 1	**Day 3**	**Day 5**	**Day 15**	**EOT [c]**
Informed reconsent [d]	X				
Complete physical examination					X
Symptom-directed physical examination [e]	X				
Weight [f]	X [f]				X
ECOG performance status	X				X
Vital signs [g]	X	X	X		X
12-lead ECG [h]	X				X
Pregnancy test [i]	X				X
Hematology [j]	X		X	X [j]	X
Coagulation [k]	X				X
Complete chemistry panel [j,l]	X		X	X [l]	X
Select chemistry panel [j,m]		X			
Urinalysis with microscopic analysis [n]					X
BMA/biopsy and investigator disease assessment [o]	Collect BMA at suspected relapse [o]				
SAE collection [p]	SAEs (including serious pretreatment events) will be reported from the time informed consent is signed through 30 days after the last dose of any study drug.				
AE collection	Recorded from the first dose of any study drug through 30 days after the last dose of any study drug. 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.				
Study Drug Administration: Combination Azacitidine, Venetoclax, and Pevonedistat or Venetoclax Plus Azacitidine [q, r, s]					
Azacitidine administration [t]	Days 1 through 7 of each cycle **or** Days 1 through 5, 8, and 9				
Venetoclax administration	Days 1 through 28 of Cycle 1; Days 1 through 28 Cycle 2 and beyond				
Pevonedistat infusion [t]	Days 1, 3, and 5 of each cycle				

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BMA: bone marrow aspirate; BSA: body surface area; BUN: blood urea nitrogen; COVID-19: coronavirus disease 2019; C1D1: Cycle 1 Day 1; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EDC: electronic data capture; EOT: end of treatment; IEC: independent ethics committee; IRB: independent review board; IV: intravenous(ly); LDH: lactate dehydrogenase; PO: oral administration (orally); PT: prothrombin time; SAE: serious adverse event; SC: subcutaneous(ly); SOE: Schedule of Events; TEAE: treatment-emergent adverse event.

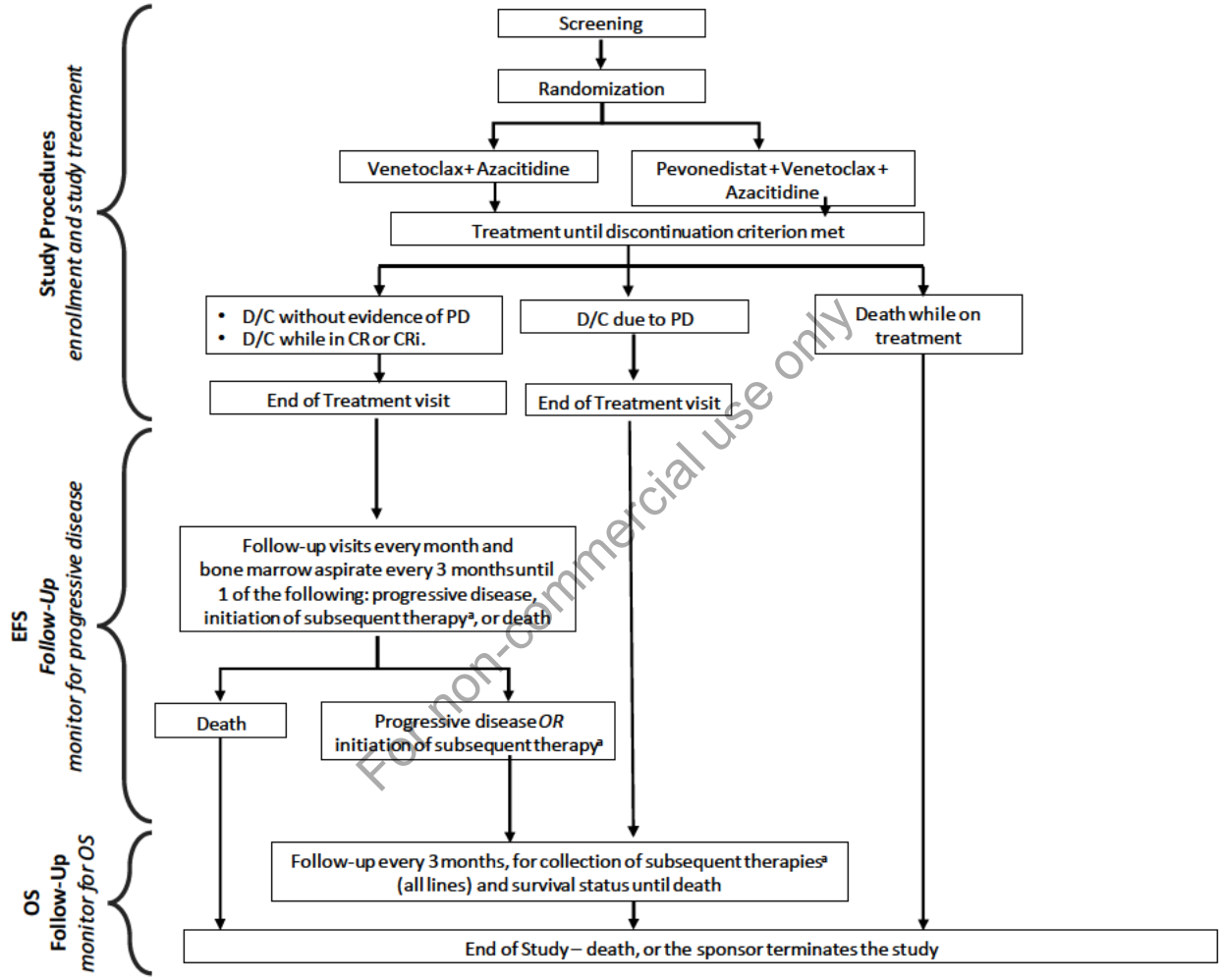
Nonessential protocol visits that do not require on-site sample collection and assessment may be completed via telemedicine (video or phone conversation between the patient and the treating physician, if allowed per institutional and local guidelines) in situations where a site visit cannot be conducted,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

	Treatment Cycle (28 Days) [a, b]				
	Day 1	Day 3	Day 5	Day 15	EOT [c]

(eg, COVID-19–related) and the assessments performed are to be captured in the EDC.
[a] On dosing days, all procedures are to be performed before dosing, unless specified otherwise.
[b] For a new cycle of treatment with study drugs to begin, toxicities considered to be related to treatment with study drugs must have resolved to Grade ≤1 or patient's baseline, as defined in Section 8.3.
[c] 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.
[d] Before dosing on Day 1 of the next full treatment cycle upon implementation of this modified SOE, patients must be reconsented (Section 9.4.2). Reconsenting should be done in person.
[e] Symptom-directed physical examination should be taken within 2 days of Day 1 of each cycle per standard of care.
[f] 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 F) on C1D1, 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.
[g] Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected at screening, predose on Days 1, 3, and 5 on each treatment arm of each treatment cycle, at EOT, and as clinically indicated. Vital sign measurements will be taken with the patient in the supine or sitting position.
[h] ECG will be performed prior to study dose administration on Day 1 in each treatment cycle. Additional ECGs may be performed as clinically indicated.
[i] A pregnancy test must 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.
[j] Clinical laboratory evaluations will be performed by a local laboratory. All central laboratory assessments are discontinued. Patients should be assessed and treated according to standard of care using local laboratory evaluations. Abnormal hematology and chemistry data are to be collected and recorded in the eCRF only to the extent that they are needed to document or support an AE. Laboratory assessments to inform dosing decisions and routinely monitor patients do not need to be recorded in the eCRF.
[k] Coagulation panel includes PT and aPTT (to be performed by the central laboratory). Coagulation samples will be collected up to 3 days before Day 1 dosing in each treatment cycle and at EOT.
[l] The complete chemistry panel will include the following: BUN, creatinine, sodium, potassium, chloride, carbon dioxide, glucose, blood uric acid, total bilirubin, direct bilirubin, ALP, LDH, AST, ALT, albumin, magnesium, phosphate, and calcium.
[m] The select chemistry panel will include: BUN, creatinine, blood phosphate, total bilirubin, ALP, AST, and ALT.
[n] 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. Samples will be analyzed by a central laboratory.
[o] BMA samples will be collected for bone marrow blast count (local analyses) as clinically indicated. If relapse is suspected and a BMA sample is collected per standard of care, a portion of the sample may be used for additional disease assessment by the sponsor.
[p] SAEs will be entered in the eCRF. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).
[q] Investigational pevonedistat + venetoclax + azacitidine arm (Arm A) only: See Section 8.10 for pevonedistat dosing instructions.
[r] All patients will receive azacitidine 75 mg/m^2 IV or SC on Days 1 through 7 of each cycle **or** Days 1 through 5, 8, and 9 in accordance with Section 8.1.
[s] All patients will receive venetoclax 400 mg PO daily on Days 1 through 28 of a 28-day cycle.
[t] In the Investigational Arm A (pevonedistat + venetoclax + azacitidine), azacitidine will be administered first followed by pevonedistat.

Appendix B Study Diagram

The Modified Schedule of Events (Appendix A) will be followed after implementation of Protocol Amendment 4. Long-term follow up visits (EFS/response and OS) will no longer be required; patients will complete an End of Treatment visit 30 (+10) days after the last dose of study drug(s) or before the start of antineoplastic therapy if that occurs sooner.



AE: adverse events; CR: complete response/remission; CRi: complete remission with incomplete blood count recovery; D/C: discontinuation; EFS: event-free survival; OS: overall survival; PD: progressive disease.

[a] Subsequent therapy is defined as agent(s) with antileukemic activity.

Appendix C Responsibilities of the Investigator

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

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

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

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

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

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, 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.

The 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 the 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.

The 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 the investigator's own country.

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

Appendix E 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, 1982 [36].
ECOG: Eastern Cooperative Oncology Group.

Appendix F Body Surface Area

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

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

OR

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

Appendix G Excluded Moderate and Strong CYP3A Inducers

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

In Vivo Inducers of CYP3A

Moderate Inducers: 50%-80% Decrease in AUC	Strong Inducers: ≥80% Decrease in AUC
Bosentan	Carbamazepine
Efavirenz	Phenytoin
Modafinil	Phenobarbital
	Primidone
	Rifabutin
	Rifampin
	Rifapentine
	St. John's Wort

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

Appendix H New York Heart Association Classification of Cardiac Disease

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

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

Source: New York Heart Association [37].

Appendix I 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: Etienne et al, 2007 [38].

Appendix J 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

Appendix K Modification of Diet in Renal Disease Study Equation

eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr, std})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American).

Where, eGFR is estimated glomerular filtration rate; S_{cr} is serum creatinine.

The eGFR calculated above will be an estimate of creatinine clearance.

Appendix L Schedule of Events

Upon implementation of Protocol Amendment 4, the modified SOEschedule of events (Appendix A) will be followed for patients continuing on the study.

	Screening [a,b]	Treatment Cycle (28 Days) [c,d,e]										Follow-up		
		Cycle 1						Cycle 2 and beyond				EFS [f]	Response [g]	OS
	Days	1	3	5	8	15	21	1	3	5	EOT [h]	Every Month	Upon PD or Suspected Relapse or Relapse	Every 3 Months
Procedures Window						±1 Day	±1 Day				+10 Days	±2 Weeks	±2 Weeks	±2 Weeks
Informed consent	X													
Inclusion/exclusion [i]	X													
Demographics	X													
Complete medical history	X													
Modified Charlson comorbidity index assessment [j]	X													
Complete physical examination	X										X			
Symptom-directed physical examination [k]		X						X				X	X	
Height	X													
Weight [l]	X	X [l]						X [l]			X			
ECOG performance status	X							X			X			
Vital signs [m]	X	X	X	X				X	X	X	X			
12-lead ECG [n]	X	X						X			X			
Chest x-ray [o]	X													
Pregnancy test [p]	X	X						X			X			
Hematology [q]	X	X	X	X	X	X	X	X		X	X	X	X	
Coagulation [r]	X	X						X			X			
Complete chemistry panel [q,s]	X	X	X	X				X		X	X	X	X	
Select chemistry panel [q,t]					X	X	X		X					
Reticulocyte count and ferritin [u]	X	X						X			X			
Urinalysis with microscopic analysis [v]	X										X			
EORTC-QLQ-C30 [w] and supplemental items	X	X						X			X	X	X	

	Screening [a,b]	Treatment Cycle (28 Days) [c,d,e]										Follow-up		
		Cycle 1						Cycle 2 and beyond				EFS [f]	Response [g]	OS
	Days	1	3	5	8	15	21	1	3	5	EOT [h]	Every Month	Upon PD or Suspected Relapse or Relapse	Every 3 Months
Procedures Window						±1 Day	±1 Day				+10 Days	±2 Weeks	±2 Weeks	±2 Weeks
EQ-5D-5L [w]	X	X						X			X	X	X	
Hospitalization assessment [w]		X						X			X	X	X	
Plasma samples for pevonedistat PK		X	X [x]	X [x]				X [y]						
Blood samples for RNA [z]		X												
Plasma samples for circulating biomarkers [aa]		X											X	
Blood samples for MOA and LSCs [bb]		X						X					X	
BMA/biopsy and investigator disease assessment	See Appendix L, Table 1 for Bone Marrow Collection and Assessment Schedule													
Serum sample for circulating biomarkers [cc]		X						X					X	
SAE collection [dd]	SAEs including serious pretreatment events will be reported from the time informed consent is signed through 30 days after the last dose of any study drug.													
AE collection		Recorded from the first dose of any study drug through 30 days after the last dose of any study drug. 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 [ee]											X	X	X	X
Survival follow-up contact														X
Study Drug Administration: Combination Azacitidine, Venetoclax, and Pevonedistat or Venetoclax Plus Azacitidine [c,ff,gg,hh]														
Azacitidine administration [ii]		Days 1 through 7 of each cycle **or** Days 1 through 5, 8, and 9												
Venetoclax administration		Days 1 through 28 of Cycle 1; Days 1 through 28 Cycle 2 and beyond												
Pevonedistat infusion [ii]		Days 1, 3, and 5 of each cycle												

	Screening [a,b]	Treatment Cycle (28 Days) [c,d,e]										Follow-up		
		Cycle 1						Cycle 2 and beyond				EFS [f]	Response [g]	OS
	Days	1	3	5	8	15	21	1	3	5	EOT [h]	Every Month	Upon PD or Suspected Relapse or Relapse	Every 3 Months
Procedures Window						±1 Day	±1 Day				+10 Days	±2 Weeks	±2 Weeks	±2 Weeks

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AML: acute myeloid leukemia; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BMA: bone marrow aspirate; BSA: body surface area; BUN: blood urea nitrogen; C1D1: Cycle 1 Day 1; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EFS: event-free survival; EORTC-QLQ-C30 European Organisation for the Research and Treatment of Cancer Core Quality of Life Questionnaire; EOT: end of treatment; EQ-5D-5L: EuroQoL 5 dimensions 5 levels; HRQOL: health-related quality of life; IEC: independent ethics committee; IRB: independent review board; IV: intravenous(ly); LDH: lactate dehydrogenase; LSC: leukemic stem cell; MOA: mechanism of action; OS: overall survival; PD: progressive disease; PK: pharmacokinetics; PT: prothrombin time; RBC: red blood cell; SAE: serious adverse event; SC: subcutaneous(ly); TLS: tumor lysis syndrome.

Nonessential protocol visits that do not require on-site sample collection and assessment may be completed via telemedicine (video or phone conversation between the patient and the treating physician, if allowed per institutional and local guidelines) in situations where a site visit cannot be conducted, such as in a COVID-19 pandemic. The reason for telemedicine (eg, COVID-19–related) and the assessments performed are to be captured in the electronic data capture (EDC).

[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 C1D1 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 dosing unless specified otherwise.

[d] For a new cycle of treatment with study drugs to begin, toxicities considered to be related to treatment with study drugs must have resolved to Grade ≤1 or patient's baseline, as defined in Section 8.3.

[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 drugs 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 of azacitidine should not be exceeded. If dosing is adjusted, study procedures should be performed on the actual day of dosing.

[f] EFS follow-up is monthly, but BMA is taken during the beginning of the EFS follow-up and then once every 3 months thereafter, or upon suspected relapse from CR or CRi.

[g] Response visits apply to patients whom have discontinued treatment for a reason other than PD.

[h] The EOT visit will occur 30 days (+10 days) after the last dose of study drug(s) or before the start of subsequent antineoplastic therapy if that occurs sooner. After the EOT visit, patients will enter EFS follow-up if their disease has not progressed and they have not started subsequent therapy. Patients will enter OS follow-up when they have started subsequent therapy.

[i] Confirmation of patient eligibility by the study medical monitor is required prior to randomization. A patient eligibility checklist must be completed and submitted by the investigator for review and approval by the sponsor or designee prior to patient randomization.

[j] See Appendix I for the modified Charlson comorbidity index.

[k] Symptom-directed physical examination should be taken within 2 days of Day 1 of each cycle per standard of care.

[l] 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 F) on C1D1, 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.

	Screening [a,b]	Treatment Cycle (28 Days) [c,d,e]										Follow-up		
		Cycle 1						Cycle 2 and beyond				EFS [f]	Response [g]	OS
	Days	1	3	5	8	15	21	1	3	5	EOT [h]	Every Month	Upon PD or Suspected Relapse or Relapse	Every 3 Months
Procedures Window						±1 Day	±1 Day				+10 Days	±2 Weeks	±2 Weeks	±2 Weeks

[m] Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected at screening, predose on Days 1, 3, and 5 on each treatment arm of each treatment cycle, at EOT, and as clinically indicated. Vital sign measurements will be taken with the patient in the supine or sitting position.
[n] ECG will be performed prior to study dose administration on Day 1 in each treatment cycle. Additional ECGs may be performed as clinically indicated. Note: Echocardiogram or multigated acquisition (MUGA) scan will be performed at screening if data for these is not available within 3 months of screening.
[o] If a chest x-ray or chest CT scan was performed within 2 months prior to randomization, the chest x-ray does not need to be performed during screening.
[p] 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.
[q] Clinical laboratory evaluations will be performed by a central laboratory. The central laboratory results should be used for determination of eligibility by the sponsor's project clinician (or designee) prior to randomization. For dosing decisions and/or safety concerns, local hematology and chemistry results should be used; however, samples must still be sent to the central lab as well. Hematology and chemistry samples may be collected up to 3 days before Day 1 dosing and 24 hours before Days 3 and 5 dosing, when required. Local laboratory evaluations may be done more frequently at the investigator's discretion. **Note: An additional sample for hematology evaluation will be collected on Cycle 2 Day 15.**
[r] Coagulation panel includes PT and aPTT (to be performed by the central laboratory). Coagulation samples will be collected up to 3 days before Day 1 dosing in each treatment cycle and at EOT.
[s] The complete chemistry panel will include the following: BUN, creatinine, sodium, potassium, chloride, carbon dioxide, glucose, blood uric acid, total bilirubin, direct bilirubin, ALP, LDH, AST, ALT, albumin, magnesium, phosphate, and calcium. **Note: An additional sample for complete chemistry evaluation will be collected on Cycle 2 Day 15**. The TLS panel will include calcium, phospate, potassium, blood uric acid and creatinine. **TLS panel will be done at a local laboratory at predose on Day 1 of venetoclax dosing and at predose on Day 1 of each new venetoclax dose level (see Section 8.1). TLS panel will be checked between 4 to 12 hours after each new venetoclax dose level (ie, during the venetoclax ramp-up), and 24 hours after reaching final dose (see Section 8.7.3).**
[t] The select chemistry panel will include the following: BUN, creatinine, blood phosphate, total bilirubin, ALP, AST, and ALT.
[u] 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.
[v] 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.
[w] 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 drugs administered. The EORTC-QLQ-C30 and EQ-5D-5L will be completed.
[x] Investigational pevonedistat + venetoclax + azacitidine (Arm A) only: blood samples for the determination of pevonedistat plasma concentrations will be collected during Cycle 1 at the following time points: Day 1 at the end of the pevonedistat infusion (immediately before stopping the infusion), at 1.5 hours (±30 minutes) and at 4 hours (± 45 minutes) after completion of the pevonedistat infusion; Day 3 at the end of the pevonedistat infusion (immediately before stopping the infusion); and Day 5 predose (within 10 minutes before azacitidine dosing), at the end of the pevonedistat infusion (immediately before stopping the infusion), and at 4 hours (± 45 minutes) after completion of the pevonedistat infusion. The

	Screening [a,b]	Treatment Cycle (28 Days) [c,d,e]										Follow-up		
		Cycle 1						Cycle 2 and beyond				EFS [f]	Response [g]	OS
	Days	1	3	5	8	15	21	1	3	5	EOT [h]	Every Month	Upon PD or Suspected Relapse or Relapse	Every 3 Months
Procedures Window						±1 Day	±1 Day				+10 Days	±2 Weeks	±2 Weeks	±2 Weeks

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] Investigational pevonedistat + venetoclax + azacitidine (Arm A) only: blood samples 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). 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.

[z] Investigational pevonedistat + venetoclax + azacitidine treatment arm (Arm A) only: Blood samples for RNA will be collected at C1D1 prior to study dose administration, at 4 hours (±45 minutes) and 8 hours (±45 minutes) after completion of the pevonedistat infusion.

[aa] Plasma samples for circulating biomarkers will be collected C1D1 prior to study dose administration, at 4 hours (±45 minutes) and 8 hours (±45 minutes) postdose and at suspected relapse or relapse in both treatment arms. The exact date and time of each sample collection should be recorded accurately. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

[bb] Blood samples for MOA and LSCs will be collected on C1D1 at predose and 4 hours postdose and on C2D1 and C4D1 at predose and 3 hours postdose and at suspected relapse or relapse in both treatment arms. Use the same methodology for this assessment throughout the study. The exact date and time of each sample collection should be recorded accurately. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

[cc] Serum sample for circulating biomarkers. Blood samples for serum biomarker analysis will be collected at C1D1 before study dose administration and at 8 hours (±45 minutes) postdose and on C2D1 at predose and 3 hours postdose and at suspected relapse or relapse in both treatment arms.

[dd] SAEs will be entered in the eCRF. Serious pretreatment events (occurring before the first dose of any study drug) will be reported to the Takeda Global Pharmacovigilance Department (or designee) and will be recorded in the eCRF. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

[ee] Subsequent therapy is defined as an agent(s) with antileukemic activity.

[ff] Investigational pevonedistat + venetoclax + azacitidine arm (Arm A) only: See Section 8.10 for pevonedistat dosing instructions. Subsequent pevonedistat doses may be reduced because of toxicity in accordance with Section 8.3.3.1 (nonhematologic toxicities) and Section 8.3.2.1 (hematologic toxicities).

[gg] All patients will receive azacitidine 75 mg/m^2 IV or SC on Days 1 through 7 of each cycle **or** Days 1 through 5, 8, and 9 in accordance with Section 8.1. The azacitidine dose may be reduced due to toxicity in accordance with Section 8.3.2.3.

[hh] During Cycle 1 only, venetoclax will be administered at the ramp-up doses of 100 mg on Day 1, 200 mg on Day 2, and 400 mg Days 3 through 28. From Cycle 2 and subsequent cycles, all patients will receive venetoclax 400 mg PO daily on Days 1 through 28 of a 28-day cycle. If remission is confirmed in Cycle 1 or thereafter, Venetoclax (400 mg) can be administered on Days 1 through 21 of a 28-day cycle in subsequent cycles, to prevent potential prolonged myelosuppression and treatment delays. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles.

[ii] In the investigational arm, azacitidine will be administered first followed by pevonedistat.

Table 1 Bone Marrow Collection and Assessment Schedule

Assessment	Screening	Cycle 1	Cycle 3	Cycle 6	Cycle 9	Suspected Relapse or Relapse	EFS/Response Follow-up (Every 3 Months)
Bone marrow blast count (local and central analyses)	X [a]	X [b]	X [b,c]	X [b,c]	X [b,c]	X	X [c]
Fresh BMA sample for molecular analysis (MOA and LSCs enumeration)	X [d]	X [d]	X [d]	X [d]	X [d]	X [e]	
Fresh BMA sample for molecular analysis, MRD, and cytogenetic risk category	X [d,f]	X [d]	X [d]	X [d]	X [d]	X [e]	
Mutation analysis (local analysis report only)	X [g]						
Locally generated pathology report	X [f]						
Locally generated cytogenetic report	X [f]						

BMA: bone marrow aspirate; CR: complete remission; CRi: complete remission with incomplete blood count recovery; eCRF: electronic case report form; EFS: event-free survival; LSC: leukemic stem cell; MOA: mechanism of action; MRD: measurable residual disease; PCR: polymerase chain reaction; PD: progressive disease.

[a] BMA will be collected at screening and indicated time points (up to -7 days), at relapse or PD, and as clinically indicated (see Section 9.4.20.1 for detailed examples). A bone marrow biopsy may be collected only at screening to confirm the diagnosis. A bone marrow biopsy may be collected with BMA in accordance with institutional guidelines. If a biopsy was performed within 28 days before randomization, this archival sample may be used to confirm diagnosis and does not need to be repeated. However, a BMA for molecular analysis is still required at screening (see footnote d below). The bone marrow pathology report(s) will be submitted to the central laboratory.

[b] A BMA for blast count (to inform disease burden assessment) will be performed at screening, Cycle 1, Cycle 3, and every 3 cycles thereafter, or at suspected relapse or relapse. Results must be available before dosing starts in the next cycle.

[c] For patients who achieve CR at any cycle, BMA will be performed only as clinically indicated or at suspected relapse or at relapse. Additional BMA may be performed if warranted by changes in peripheral blood counts.

[d] Fresh BMA will be obtained at screening, Cycle 1, Cycle 3, and every 3 cycles thereafter, or at suspected relapse or at relapse for baseline and longitudinal molecular characterization. For patients who achieve CR at any cycle, BMA will be performed only as clinically indicated or at suspected relapse or at relapse. Patients who achieve a CR are encouraged, but not required, to have a BMA on the indicated time points. Patients who have a CRi are required to have BMA on the indicated time points. BMA samples will be sent to a central laboratory for molecular analysis.

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

Table 1 Bone Marrow Collection and Assessment Schedule

Assessment	Screening	Cycle 1	Cycle 3	Cycle 6	Cycle 9	Suspected Relapse or Relapse	EFS/Response Follow-up (Every 3 Months)

[f] Cytogenetics analysis will be done at a central laboratory. A BMA sample taken within 28 days of randomization will be shipped for analysis at the central laboratory (per instructions in the Laboratory Manual). In addition, whenever cytogenetic analysis is performed locally at the clinical site the cytogenetic report(s)/pathology report(s) will be submitted to the central laboratory.

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

Appendix M Protocol History

Amendment History:

Date	Amendment No.	Amendment Type	Region
21 January 2022	4	Substantial	Global
08 July 2021	3	Substantial (not implemented)	Global
28 July 2020	2	Substantial	Global
10 July 2020	1	Substantial	Global
21 November 2019	Initial Protocol	Not applicable	Global

Protocol Amendment 3 Summary and Rationale:

Protocol Amendment 3 (dated 08 July 2021), which converted the phase 2 study to a registration-enabling phase 3 study and included a change in the primary endpoint, expansion of sample size, and increase in number of sites, will not be implemented. Thus, the changes in reference to the protocol incorporating Amendment 3 are not shown here.

Rationale for Amendment 2

This document describes the changes in reference to the protocol incorporating Amendment 2. The primary reason for this amendment is to incorporate changes requested by Global Health Authorities.

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

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
1. Updated dose modification guidelines for drug-related toxicity to include toxicity at least possibly related to study drug	Change made in response to protocol review by Global Health Authorities	Section 8.3.1.1 Retreatment Within a Cycle
2. Updated dose modification guidelines for drug-related toxicity of Grade 3 to 4 at least possibly related to study drug	Change made in response to protocol review by Global Health Authorities	Section 8.3.3.1 Pevonedistat Paragraph relating to Pevonedistat Dose Adjustment for Other Toxicities
3. Required additional hematology panel on Day 15 of Cycle 2	Change made in response to protocol review by Global Health Authorities	Appendix A Schedule of Events, footnote “q”
4. Required additional complete chemistry panel on Day 15 of Cycle 2	Change made in response to protocol review by Global Health Authorities	Appendix A Schedule of Events, footnote “s”

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
5. Defined tumor lysis syndrome (TLS) panel	Provided analytes in TLS in Clinical Laboratory Evaluations section of the protocol	Section 9.4.18 Clinical Laboratory Evaluations and Table 9.b Complete Serum Chemistry and Tumor Lysis Syndrome Panels
6. Added potassium to TLS panel and clarified TLS collection times relative to venetoclax dosing	Updated missing analyte and included the collection times in the Schedule of Events for consistency with text in the body of the protocol	Appendix A Schedule of Events, footnote "s"
7. Updated citations for US Prescribing Information and Summary of Product Characteristics for venetoclax and azacitidine	Editorial update to provide current information	Section 16.0 REFERENCES and throughout the document

Rationale for Amendment 1

This document describes the changes in reference to the protocol incorporating Amendment 1. The primary reason for this amendment is to incorporate changes requested by Global Health Authorities.

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

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
1. Clarified use of strong cytochrome P450 (CYP)3A inhibitors	Change made in response to protocol review by Global Health Authorities	Section 4.7.2.3 Drug Interactions Section 8.3.1.3 Venetoclax Dosing With CYP3A4 Inducers and Inhibitors Table 8.d Management of Potential Venetoclax Interactions With CYP3A and P-gp Inhibitors for Patients With AML
2. Clarified criteria for resumption of therapy after toxicity in initiation of new cycle of treatment	Change made in response to protocol review by Global Health Authorities	Section 8.3.1.2 Initiation of a New Cycle

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
3. Added guidance in a new protocol section on management of cytopenia and infection	Change made in response to protocol review by Global Health Authorities	Section 8.7.5 Management of Cytopenia and Infection
4. Specified that nonessential protocol visits that do not require on-site sample collection and assessment may be completed via telemedicine	Provide general guidance	Section 9.4 Study Procedures Appendix A Schedule of Events, Note below Table
5. Required additional coagulation panel tests on Day 1 of each treatment cycle	Change made in response to protocol review by Global Health Authorities	Section 9.4.18 Clinical Laboratory Evaluations Appendix A Schedule of Events
6. Required additional ECG measurement on Day 1 of each treatment cycle	Change made in response to protocol review by Global Health Authorities	Appendix A Schedule of Events
7. Revised the timeframe of contraception (and donation of eggs) in women of childbearing potential from 4 months to 6 months	Change made in response to protocol review by Global Health Authorities	Section 7.1 Inclusion Criteria Section 7.2 Exclusion Criteria Section 8.6 Precautions and Restrictions
8. Updated Sponsor contact information	Updated Corporate name and change of headquarter location	Title Page Section 2.0 Study Summary Section 3.4 Corporate Identification
9. Deleted exploratory objective and endpoint related to potential of a biomarker based on the mutation status of select AML genes	The biomarker was found to lack predictive ability in a previous study and its predictive potential to the triple combination was no longer considered valid	Section 5.1.4 Exploratory Objectives Section 5.2.4 Exploratory Endpoints
10. Updated number of sites to approximately 85 globally (increased from approximately 70 sites globally)	Allow flexibility and faster enrollment into the study	Section 2.0 Study Summary Section 6.2 Number of Patients

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
11. Clarified venetoclax dosing information for Cycle 1 and subsequent cycles (provided dosing guidelines in case of confirmed remission or if venetoclax is well tolerated)	Change made in response to protocol review by Global Health Authorities	Section 2.0 Study Summary Section 4.6.4 Rationale for Dose and Schedule of Study Drugs Section 6.1 Overview of Study Design Section 8.1Study Drug Administration: Pevonedistat With Venetoclax and Azacitidine Section 8.2 Reference/Control Therapy: Venetoclax Plus Azacitidine Appendix A Schedule of Events
12. Modified inclusion criteria to avoid enrolling patients with not suitable intensive chemotherapy	Change made in response to protocol review by Global Health Authorities	Section 2.0 Study Summary Section 7.1 Inclusion Criteria, criterion #3
13. Defined supraphysiologic doses of corticosteroids (>10 mg/d prednisone or equivalent)	Increase clarity	Section 8.4 Excluded Concomitant Medications and Procedures, Table 8.c
14. Clarified sequence of drug administrations in the investigational arm	Increase clarity	Section 8.1 Study Drug Administration: Pevonedistat With Venetoclax and Azacitidine Appendix A Schedule of Events, footnote "ii"
15. Clarified the role of Central and Local Laboratories	Increase clarity	Section 9.4.18 Clinical Laboratory Evaluations
16. Added echocardiogram or multigated acquisition scan and their timeframe	Change made in response to protocol review by Global Health Authorities	Section 7.2 Exclusion Criteria Section 9.4.12 ECG Appendix A Schedule of Events
17. Required additional hematology panel on Day 5 of subsequent cycles, complete chemistry panel on Cycle 1 Days 1 and 5 and on Day 5 of subsequent cycles, and additional time points for Coagulation were added	Change made in response to protocol review by Global Health Authorities	Appendix A Schedule of Events, including footnote "r"
18. Added tumor lysis syndrome chemistry panel to chemistry panel in Cycle 1	Change made in response to protocol review by Global Health Authorities	Appendix A Schedule of Events

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
19. Added dose modification language for azacitidine based on serum levels of bicarbonate, blood urea nitrogen or creatinine	Change made in response to protocol review by Global Health Authorities	Section 8.7.1 Azacitidine
20. Clarified time points for collection of bone marrow aspirate and bone marrow biopsy	Increase clarity	Section 6.1 Overview of Study Design Appendix A Schedule of Events, Table 1, footnote "a"
21. Indicated that Modification of Diet in Renal Disease Study equation should be used for calculation of creatinine clearance (not Cockcroft-Gault formula)	Updated procedural change	Section 2.0 Study Summary Section 7.1 Inclusion Criteria, criterion #4 Section 9.4.18 Clinical Laboratory Evaluations Appendix K Modification of Diet in Renal Disease Study Equation
22. Indicated that an initial safety assessment will be performed after 10 patients have completed at least 1 cycle of treatment	Change made in response to protocol review by Global Health Authorities	Section 11.3 Takeda Safety Monitoring

Amendment 4 to A Randomized, Open-label, Controlled, Phase 2 Study of Pevonedistat, Venetoclax, and Azacitidine Versus Venetoclax Plus Azacitidine in Adults With Newly Diagnosed Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	21-Jan-2022 15:35 UTC
[redacted]	Biostatistics Approval	21-Jan-2022 17:39 UTC