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

Published: 28-12-2015
Last updated: 20-04-2024

Primary• To determine in patients with higher-risk myelodysplastic syndrome (HR MDS), chronic myelomonocytic leukemia (CMML), and low-blast acute myelogenous leukemia (AML) whether the combination of pevonedistat and azacitidine improves event-free...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Leukaemias |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON45865

**Source**
ToetsingOnline

**Brief title**
P-2001

### Condition

- Leukaemias

**Synonym**
cancer, Leukemia

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Millennium Pharmaceuticals, Inc. (Takeda)
**Source(s) of monetary or material Support:** farmaceutische industrie

## Intervention

**Keyword:** Azacitidine, Leukemia, Pevonedistat

## Outcome measures

### Primary outcome

EFS; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death or disease progression (see Section 7.4.21).

### Secondary outcome

• OS.

• Six-month and 1-year survival rates.

• Time to AML transformation in HR MDS and CMML patients.

• CR, CR+PR, overall response (CR+PR+HI for HR MDS and CMML; CR+PR for low-blast AML).

• CR, CR+PR, overall response (CR+PR+HI for HR MDS and CMML; CR+PR for low-blast AML) by Cycle 4.

• Duration of CR, duration of CR+PR, duration of overall response (CR+PR+HI for HR MDS and CMML; CR+PR for low-blast AML).

• Time to first CR or PR.

• Time to subsequent therapy.

• RBCs and platelet-transfusion independence.

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

• Time to PD, relapse after CR or PR, or death.

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

# Study description

**Background summary**

MDS are commonly divided into lower- or higher-risk categories based on the Revised International Prognostic Scoring System (IPSS-R) for MDS, which is a scoring system useful for estimating overall survival and the risk of transformation to AML [1]. Overall, approximately 25% of patients with very high, high, or intermediate IPSS-R scores will transform to AML within 0.7 years, 1.4 years, and 3.2 years, respectively [1]. Median survival for patients with MDS varies from years to months and decreases with increasing IPSS-R score. Because MDS are heterogeneous diseases, varied treatment options exist. Most patients with MDS are managed with non-curative treatment strategies to control symptoms, improve quality of life, improve overall survival (OS), and decrease progression to AML. Treatment of patients with lower-risk MDS (often defined as patients with <5% myeloblasts and/or normal or good risk cytogenetics and few cytopenias) focuses on minimizing blood product transfusions and maximizing quality of life through use of supportive care (eg, antibiotics as needed for infections, red blood cell transfusions), growth factors such as erythropoiesis stimulating factors or immunosuppressive drugs. Treatment for patients with higher-risk disease often includes DNA hypomethylating agents (azacitidine and decitabine) [6]. Rarely, intensive chemotherapy is used in patients with

higher-risk MDS (HR MDS), but it generally results in significant toxicity and modest responses (uptodate.com/contents/treatment-of-high-or-very-high-risk-myelodysplastic-syndromes, Treatment of high or very high risk myelodysplastic syndromes, Accessed 08 December 2014) [7-9].
Hypomethylating agents produce objective hematologic responses in approximately half of MDS patients, delay leukemic progression, improve quality of life, and, for azacitidine only, prolong survival in HR MDS patients. Nevertheless, treatment with hypomethylating agents is not curative, and most patients relapse within 2 years. Lenalidomide, an immunomodulatory thalidomide congener, significantly improves red blood cell transfusion-independence rates and increases hemoglobin, but it is approved only for use in patients with the 5q syndrome subtype of low-risk MDS [7,8,10-12].
The only known curative therapy for MDS is allogenic stem cell transplantation. However, only a minority of patients (typically with HR MDS) undergo this procedure due to contraindications and the limited availability of appropriate stem cell donors [13]. Even in these patients, treatment-related mortality and morbidity and high relapse rates compromise long-term disease-free survival (uptodate.com/contents/treatment-of-high-or-very-high-risk-myelodysplastic-syndromes, Treatment of high or very high risk myelodysplastic syndromes, Accessed 08 December 2014) [8,14,15]. More recent therapeutic approaches to MDS patients with higher-risk disease have involved combining drugs with hypomethylating agents, either to take advantage of synergistic properties of, for example, histone deacetylase inhibition combined with epigenetic modification, or to capitalize on non-overlapping mechanisms of action [16,17].
Please consult for more information Section 1 in de protocol

**Study objective**

Primary
• To determine in patients with higher-risk myelodysplastic syndrome (HR MDS), chronic myelomonocytic leukemia (CMML), and low-blast acute myelogenous leukemia (AML) whether the combination of pevonedistat and azacitidine improves event-free survival (EFS), when compared to single-agent azacitidine; for patients with HR MDS or CMML, an event is defined as death or transformation to AML; for patients with low-blast AML, an event is defined as death or disease progression or relapse after CR.

Secondary
• To determine in patients with HR MDS, CMML, and low-blast AML, whether the combination of pevonedistat and azacitidine improves overall survival (OS) when compared to single-agent azacitidine.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves 6-month and 1-year survival rates when compared to single-agent azacitidine.
• To determine in patients with HR MDS and CMML whether the combination of

pevonedistat and azacitidine delays time to AML transformation when compared to single-agent azacitidine.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine, when compared to single agent azacitidine, improves the rate of complete remission (CR), CR plus partial remission (CR+PR), and/or overall response. Overall response in HR MDS and CMML is defined as CR+PR+hematologic improvement (HI); overall response in low-blast AML is defined as CR+PR.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine, when compared to single agent azacitidine, improves the rate of CR, CR+PR, as well as the overall response rate (ORR) by Cycle 4.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine, when compared to single-agent azacitidine, improves duration of CR, CR+PR, and/or overall response.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves time to first CR or PR when compared to single-agent azacitidine.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine delays time to subsequent therapy when compared to single-agent azacitidine. Subsequent therapy is defined as agent(s) with antileukemic/anti-myelodysplastic syndrome (MDS) activity (eg, cytarabine, anthracyclines, purine analogues, and hypomethylating agents other than azacitidine). Patients who discontinue study treatment to receive single-agent azacitidine off study would not be counted as receiving subsequent therapy.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves rate of transfusion independence when compared to single-agent azacitidine. Red blood cell (RBC) or platelet transfusion independence requires that the patient receive no RBC or platelet transfusions, respectively, for a period of at least 8 weeks.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine reduces the percent of patients who have at least one inpatient hospital admission(s) related to HR MDS, CMML, or low-blast AML when compared to single-agent azacitidine.
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine delays time to disease progression (progressive disease; PD), relapse or death when compared to single-agent azacitidine.
• To evaluate in patients with HR MDS, CMML, and low-blast AML, the safety of the combination of pevonedistat and azacitidine when compared to single-agent azacitidine.
• To collect in patients with HR MDS, CMML, and low-blast AML, plasma concentration-time data for pevonedistat to contribute to future population pharmacokinetic (PK) analyses of pevonedistat.

Exploratory
• To determine in patients with HR MDS, CMML, and low-blast AML whether the combination of pevonedistat and azacitidine improves bone marrow blast reduction by Cycle 2 and Cycle 4 when compared to single-agent azacitidine.
• To evaluate in patients with HR MDS, CMML, and low-blast AML, the potential relationship between baseline molecular characteristics of the tumor (such as cytogenetic abnormalities and somatic mutations), circulating serum biomarkers (including micro RNAs, proteins, and metabolites), and changes in gene expression and epigenetic modifications (between Screening and specified postdose time points) with the efficacy and/or safety of the combination of pevonedistat and azacitidine.
• To determine in patients with low-blast AML, the percentage of CR and CRi that are cytogenetic remissions.
• To determine minimal residual disease status in patients who achieve CR in Cycle 4 or Cycle 7 and determine its relationship to EFS.
• To evaluate in patients with HR MDS, CMML, and low-blast AML, the potential relationship between germline polymorphisms (such as in proteasome pathway genes) and the efficacy and/or safety of the combination of pevonedistat and azacitidine.
• To evaluate in patients with HR MDS, CMML, and low-blast AML, potential mechanisms of treatment-emergent resistance, such as somatic mutations in NEDD8-activating enzyme subunits and key signaling pathways, or change in pathway activity, in tumors from patients who initially respond to therapy and then exhibit progressive disease.
• To assess in patients with HR MDS, CMML, and low-blast AML, the effect on health-related quality of life (HRQOL) of the the combination of pevonedistat and azacitidine compared with single-agent azacitidine.
• To explore in patients with HR MDS, CMML, and low-blast AML, potential relationships between polymorphic variations in genes encoding drug metabolizing enzymes (DMEs) or transporters that may be implicated in pevonedistat disposition and exposure to pevonedistat.

**Study design**

This study is a multicenter, global, randomized, controlled, open-label, phase 2 clinical study of the combination of pevonedistat and azacitidine versus single-agent azacitidine administered in patients with HR MDS, CMML, or low-blast AML who have not previously received a hypomethylating agent. Once enrolled, patients will be randomized at a 1:1 ratio to receive study drug (either single-agent azacitidine or the combination of pevonedistat and azacitidine) in 28-day treatment cycles. All patients will be stratified into 4 categories: low-blast AML, Revised International Prognostic Scoring System (IPSS-R) risk group of very high, high, or intermediate for MDS/CMML [2]. All patients will receive azacitidine (75 mg/m2 [subcutaneous]) on Days 1 through 5, Day 8, and Day 9. Patients randomized to the combination arm will also receive pevonedistat (20 mg/m2 via 60 minute infusion) on Days 1, 3, and 5 of each cycle. Dose modifications may be allowed.

Patients, including those who achieve a CR, may receive study treatment until they experience unacceptable toxicity, relapse, transformation to AML, or progressive disease as defined in this study.
Patients with HR MDS or CMML may be allowed to continue study treatment (either treatment arm) if they meet the criteria for progressive disease based only on bone marrow blast count (without AML transformation) if , in the clinical judgment of the investigator , the patient is still receiving clinical benefit from this treatment and the continuation is endorsed by the sponsor*s project clinician (or designee).Patients with low-blast AML in this study may also be allowed to continue study treatment (either treatment arm), even if they meet the criteria for progressive disease based only on bone marrow blast counts, if, in the clinical judgment of the investigator, the patient is still receiving clinical benefit from this treatment, and the continuation is endorsed by the sponsor*s project clinician (or designee). Patients who meet the criteria for PD and continue on study under these conditions must be reconsented before continuing study treatment. Patients may choose to discontinue at any time.
Patients will attend the End-of-Treatment (EOT) visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner. Patients will enter EFS follow-up (study visits every 3 months, to include physical exam, clinical blood tests, HRQOL assessments, hospitalization assessment, bone marrow aspirate sampling, and disease assessment) if their disease has not transformed from HR MDS or CMML to AML (for patients with HR MDS or CMML) or progressed (patients with low-blast AML), and they have not started subsequent therapy. Patients will enter OS follow-up (contacted every 3 months to document subsequent therapies and survival status) when they have confirmed transformation to AML (for patient with HR MDS or CMML) or experienced progressive disease (patients with low-blast AML) or have started subsequent therapy.
Disease response assessments for all HR MDS and CMML patients will be based on the Modified International Working Group (IWG) response criteria for MDS [3]. Disease response assessments for low-blast AML patients will be based on the Revised Recommendations of the IWG for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [4]. Formal disease assessments for study endpoints will be determined based on local bone marrow aspirate blast counts and transfusions, and central lab data (local lab data may be used for time-sensitive clinical decisions).
Bone marrow samples (biopsy and/or aspirate) will be collected at Screening, during treatment, and during follow-up for blast count evaluation (to inform disease burden assessment). Bone marrow aspirate will also be used to analyze tumor cytogenetics, to analyze baseline somatic mutations and other molecular characteristics, to evaluate changes in epigenetic patterns, and to identify treatment emergent mutations (including biomarkers of response and resistance to the combination of pevonedistat and azacitidine, as well as biomarkers related to potential toxicity). Samples will be collected and analyzed from patients in both treatment arms.

Inpatient hospital admissions related to HR MDS, CMML, or low-blast AML, as well as RBC- and platelet-transfusion independence, will be monitored as secondary efficacy endpoints. Treatment emergent resistance will also be monitored.
Sparse sampling for the determination of pevonedistat plasma concentrations and, if appropriate, its metabolites will be collected from each patient in the Combination Pevonedistat Plus Azacitidine Arm to contribute to a population PK analysis of pevonedistat co-administered with azacitidine.
Adverse events and Eastern Cooperative Oncology Group (ECOG) performance status will be assessed, and ECGs, clinical laboratory values, and vital signs will be obtained, to evaluate the safety and tolerability of the study drug treatments.
Patient-reported HRQOL will be evaluated using the EORTC-QLQ-C30 and EQ 5D-5L (all patients) and the QOL-E (American English-speaking US patients only) questionnaires.

**Intervention**

The patient will receive azacitidine by injection under your skin on Days 1, 2, 3, 4, 5, 8 and 9. If the patient is assigned to the combination arm, the patient will also receive pevonedistat by infusion into your vein on days 1, 3 and 5 (for example, the first Monday, Wednesday and Friday of a 28-day cycle). Pevonedistat is provided as a solution for IV infusion. The infusion of pevonedistat is expected to last approximately one hour but may take longer, depending on how you tolerate it. For patients taking the combination, on Days 1, 3, and 5, when both pevonedistat and azacitidine are administered, azacitidine will be administered first, followed by pevonedistat. Safety monitoring will be done to establish the effects of pevonedistat in combination with azacitidine in your body.

**Study burden and risks**

All the assessments as stated in the protocol schedule of events are all additional in comparison with the regular treatment.

Potential Risks From Phase 1 Studies (at Doses and Schedules Substantially Higher than Currently Used in Clinical Studies)
• Single- or multi-organ failure (severe problems with the liver, kidneys, and/or heart) that could cause death. This occurred at doses and schedules that are no longer being used in current studies with pevonedistat.
• Severe problems with how your kidneys work. Many of these events occurred at doses that are no longer being used in current studies with pevonedistat.
• Abnormal heart rhythms.
• Problems with the bone marrow that could lead to increased risk of infection, bleeding and low blood counts (with or without fever).
• A reaction called an acute phase response where you may have a fever, high white blood cell levels, and a change in certain protein levels in the body.

You will be checked by your study doctor for this during the study.
• Interference with normal function of your stomach and intestine which could result in dehydration (lack of adequate water in the body), electrolyte or chemical imbalance,
• Low phosphate level in your blood. Decreased phosphate level can lead to muscle weakness and cramps, irritability, and confusion. If your phosphate levels are low, you may be given phosphate supplements either by mouth or intravenously (through the vein).
Potential Risks Possibly Due to Underlying Disease or Malignancy
• Decrease in appetite, chills (feeling cold), and/or feeling tired.
• Decreased number of white blood cells which could lead to infections
• Decreased number of white blood cells which could lead to infections, along with a fever
• Bleeding in the stomach or intestines.
• Multi-organ failure in the context of infection

Potential Risks Based on Findings From Animal Studies
• Breakdown of the heart muscle and blood clots in the heart have been seen when high doses of pevonedistat were administered
• Increased blood pressure in the artery that carries blood from the heart to the lungs.
• Changes in the heart and blood vessels that could cause a high heart rate, and high or low blood pressure.
• Degeneration of the intestines, including a reduction of body fluids and electrolytes, accompanied by a severe infection.
• Damage to your testes or ovaries which could be a risk if de patient were to have a baby and which could also result in sterility (unable to have a baby).
• If the patient or his partner were to become pregnant, there may be a risk that the fetus would not grow normally.
• Decreased bone has been seen when high doses of pevonedistat were given to animals. This may increase the risk of fractures in patients treated with pevonedistat. However, no fractures were seen in animals.
• Prolongation of one of your blood clotting measurements that may result in increased bleeding.

Your blood creatinine level is measured to check your kidney function. A small number of patients have had mild increases in creatinine, which may mean there is mild decrease in kidney function.

Benefit
It can increases the amount of time the patients live without worsening of the patients disease

# Contacts

**Public**
Millennium Pharmaceuticals, Inc. (Takeda)

Landsdowne Street 40
Cambridge 02139
US
**Scientific**
Millennium Pharmaceuticals, Inc. (Takeda)

Landsdowne Street 40
Cambridge 02139
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Male or female patients 18 years or older.
2. Morphologically confirmed diagnosis of MDS, nonproliferative CMML (ie, with WBC <20,000/µL), or low-blast AML based on 1 of the following: French-American-British (FAB) Classifications:
- Refractory anemia with excess blasts (RAEB - defined as having 5% to 20% myeloblasts in the bone marrow).
- CMML with 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood.;OR;World Health Organization (WHO) Classifications:
- Refractory anemia with excess blasts-1 (RAEB-1 - defined as having 5% to 9% myeloblasts in the bone marrow).
- Refractory anemia with excess blasts-2 (RAEB-2 - defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood).

- Chronic Myelomonocytic Leukemia-2 (CMML-2 - defined as having 10% to 19% myeloblasts in the bone marrow and/or 5% to 19% blasts in the blood).
- Chronic Myelomonocytic Leukemia-1 (Although CMML-1 is defined as having <10% myeloblasts in the bone marrow and/or <5% blasts in the blood, these patients may enroll only if bone marrow blasts >=5%).
- WHO-defined AML with 20% to 30% myeloblasts in the bone marrow (defined in this protocol as "Low-Blast AML") and < 30% myeloblasts in peripheral blood who are considered by investigator to be appropriate for azacitidine-based therapy.;3. For MDS and CMML patients, prognostic Risk Category, based on the Revised International Prognostic Scoring System (IPSS-R):
- Very high (>6 points),
- High (>4.5 - 6 points), or
- Intermediate (>3 - 4.5 points): a patient determined to be in the Intermediate Prognostic Risk Category is only allowable in the setting of >=5% bone marrow myeloblasts.
Patients with indeterminate cytogenetics findings at Screening should be assigned a cytogenetics prognostic variable of 2 points (ie, intermediate) for determining overall Prognostic Risk Category/Score
4. ECOG performance status of 0 to 2
5. Clinical laboratory values within the following parameters (repeat within 3 days before the first dose of study drug if laboratory values
used for randomization were obtained more than 3 days before the first dose of study drug):
- Albumin >2.7 g/dL.
- Total bilirubin - ALT and AST <2.5 × ULN.
- Creatinine clearance >50 mL/min
- Hemoglobin >8 g/dL. Patients may be transfused to achieve this value. Elevated indirect bilirubin due to post-transfusion hemolysis is allowed.
6. For CMML patients: WBC count <20,000/µL before administration of the first dose of study drug on Cycle 1 Day 1; patients must have been off hydroxyurea for at least 1 week prior to WBC count assessment.
7. Ability to undergo the study-required bone marrow sample collection procedures.
8. Suitable venous access for the study-required blood sampling (ie, including PK and biomarker sampling).
9. 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 methods and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
Male patients, even if surgically sterilized (ie, status postvasectomy), who:
- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation

methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
10. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

## Exclusion criteria

1. Previous treatment with decitabine or azacitidine or other hypomethylating agent.
2. Acute promyelocytic leukemia as diagnosed by morphologic examination of bone marrow, by fluorescent in situ hybridization or cytogenetics of peripheral blood or bone marrow, or by other accepted analysis.
3. Eligible for allogenic stem cell transplantation.
4. Patients with MDS, CMML, or low-blast AML, whose only site of disease is extramedullary, eg, the skin.
5. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures or could limit patient expected survival to less than 6 months.
6. Treatment with any anti-leukemic/anti-MDS therapies (eg, lenalidomide, cytarabine, anthracyclines, purine analogs) or with any investigational products within 14 days before the first dose of any study drug.
7. Known hypersensitivity to mannitol.
8. Active uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, or septicemia.
9. Major surgery within 14 days before first dose or a scheduled surgery during study period; insertion of a venous access device (eg, catheter, port) is not considered major surgery.
10. Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone resection.
11. Life-threatening illness unrelated to cancer.
12. Prothrombin time (PT) or aPTT > 1.5 ULN or active uncontrolled coagulopathy or bleeding disorder.
13. Known human immunodeficiency virus (HIV) seropositive.
14. Known hepatitis B surface antigen seropositive, or known or suspected active hepatitis C infection. Note: Patients who have isolated positive hepatitis B core antibody (ie, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load.
15. Known hepatic cirrhosis or severe pre-existing hepatic impairment.
16. Known cardiopulmonary disease defined as unstable angina, clinically significant arrhythmia, congestive heart failure (New York Heart Association [NYHA] Class III or IV; see Section 15.3), and/or myocardial infarction within 6 months prior to first dose, or severe pulmonary hypertension. As an example, well-controlled atrial fibrillation would not be an

exclusion whereas uncontrolled atrial fibrillation would be an exclusion.
17. Treatment with strong CYP3A inhibitors or inducers within 14 days before the first dose of pevonedistat.
18. Systemic antineoplastic therapy or radiotherapy for other conditions within 12 months before the first dose of any study drug, except for hydroxyurea.
19. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.
study drug.
20. Female patients who intend to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).
21. Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

# Study design

## Design

| | |
|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 03-06-2016 |
| Enrollment: | 6 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Pevonedistat |
| Generic name: | Pevonedistat |

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Vidaza |
| Generic name: | Azacitidine |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 28-12-2015 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 19-05-2016 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 20-06-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 11-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 10-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 10-04-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 02-05-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO | |

| | |
|---|---|
| Date: | 06-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2015-000221-37-NL |
| ClinicalTrials.gov | NCT02610777 |
| CCMO | NL56021.094.15 |

# Study results

Results posted: 29-08-2022

**First publication**
11-09-2020