Clinical trial results:
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

Summary

EudraCT number	2015-000221-37
Trial protocol	CZ NL ES BE DE IE BG FR IT
Global end of trial date	23 July 2021

Results information

Result version number	v1 (current)
This version publication date	28 July 2022
First version publication date	28 July 2022

Trial information

Trial identification

Sponsor protocol code	Pevonedistat-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02610777
WHO universal trial number (UTN)	U1111-1169-6540
Other trial identifiers	REec: REec-2016-2145, Israel: Pevonedistat-2001CTID

Notes:

Sponsors

Sponsor organisation name	Millennium Pharmaceuticals, Inc.
Sponsor organisation address	40 Landsdowne Street, Cambridge, MA, United States, 02139
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the efficacy and safety of pevonedistat plus azacitidine versus single-agent azacitidine in participants with HR-MDS or CMML, or low-blast AML.

Protection of trial subjects:

All the participants were required to read and sign the Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Czechia: 4
Worldwide total number of subjects	120
EEA total number of subjects	66

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	92
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 45 investigative sites in the United States [US], Canada, Belgium, Bulgaria, Czech Republic, Germany, France, Israel, Italy, Spain, and Ireland from 14 April 2016 to 23 July 2021.

Pre-assignment

Screening details:

Participants diagnosed with myelomonocytic, and myelogenous leukemia were randomized into two groups in 1:1 ratio to receive single-agent azacitidine or azacitidine + pevonedistat.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Azacitidine 75 mg/m^2

Arm description:

Azacitidine 75 mg/m^2, infusion, intravenously or subcutaneously, on Day 1 through Day 5, Days 8 and 9 in 28-day treatment cycles until unacceptable toxicity, relapse, transformation to AML (for participants with HR MDS or CMML), or progressive disease (for participants with low-blast AML).

Arm type	Active comparator
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Azacitidine intravenous or subcutaneous formulation.

Arm title	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Arm description:

Azacitidine 75 mg/m^2, infusion, intravenously or subcutaneously, on Day 1 through Day 5, Days 8 and 9 and pevonedistat 20 mg/m^2, infusion, intravenously, on Days 1, 3, and 5 in 28-day treatment cycles until unacceptable toxicity, relapse, transformation to AML (for participants with HR MDS or CMML), or progressive disease (for participants with low-blast AML).

Arm type	Experimental
Investigational medicinal product name	Pevonedistat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Pevonedistat intravenous or subcutaneous formulation.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:
Azacitidine intravenous or subcutaneous formulation.

Number of subjects in period 1	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2
Started	62	58
Response Evaluable Population (REP)	53	55
Completed	0	0
Not completed	62	58
Adverse event, serious fatal	50	47
Consent withdrawn by subject	2	2
Site Terminated by Sponsor	9	8
Lost to follow-up	1	-
Reason not Specified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Azacitidine 75 mg/m^2
Reporting group description:	
Azacitidine 75 mg/m^2, infusion, intravenously or subcutaneously, on Day 1 through Day 5, Days 8 and 9 in 28-day treatment cycles until unacceptable toxicity, relapse, transformation to AML (for participants with HR MDS or CMML), or progressive disease (for participants with low-blast AML).	
Reporting group title	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2
Reporting group description:	
Azacitidine 75 mg/m^2, infusion, intravenously or subcutaneously, on Day 1 through Day 5, Days 8 and 9 and pevonedistat 20 mg/m^2, infusion, intravenously, on Days 1, 3, and 5 in 28-day treatment cycles until unacceptable toxicity, relapse, transformation to AML (for participants with HR MDS or CMML), or progressive disease (for participants with low-blast AML).	

Reporting group values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2	Total
Number of subjects	62	58	120
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	69.5	71.7	
standard deviation	± 8.87	± 9.63	-
Gender categorical Units: Subjects			
Male	21	16	37
Female	41	42	83
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	4	7
Not Hispanic or Latino	55	52	107
Unknown or Not Reported	4	2	6
Race (NIH/OMB) Units: Subjects			
Asian	3	1	4
Black or African American	3	2	5
White	54	52	106
Unknown or Not Reported	2	3	5
Height Units: centimeter (cm)			
arithmetic mean	169.12	168.87	
standard deviation	± 10.857	± 7.510	-
Body Surface Area Units: square meter (m^2)			
arithmetic mean	1.92	1.88	
standard deviation	± 0.265	± 0.201	-
Weight			

Units: kilogram (kg)			
arithmetic mean	79.19	75.95	
standard deviation	± 18.471	± 13.716	-

End points

End points reporting groups

Reporting group title	Azacitidine 75 mg/m^2
Reporting group description:	
Azacitidine 75 mg/m^2, infusion, intravenously or subcutaneously, on Day 1 through Day 5, Days 8 and 9 in 28-day treatment cycles until unacceptable toxicity, relapse, transformation to AML (for participants with HR MDS or CMML), or progressive disease (for participants with low-blast AML).	
Reporting group title	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2
Reporting group description:	
Azacitidine 75 mg/m^2, infusion, intravenously or subcutaneously, on Day 1 through Day 5, Days 8 and 9 and pevonedistat 20 mg/m^2, infusion, intravenously, on Days 1, 3, and 5 in 28-day treatment cycles until unacceptable toxicity, relapse, transformation to AML (for participants with HR MDS or CMML), or progressive disease (for participants with low-blast AML).	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from the date of randomization to the date of death due to any cause. Participants without documented death at the time of the analysis were censored at the date the participant was last known to be alive. The Kaplan Meier estimates was used for the analysis. ITT Population was defined as all participants who were randomized.	
End point type	Primary
End point timeframe:	
From date of randomization until death (up to approximately 5 years)	

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: months				
median (confidence interval 95%)	19.0 (13.57 to 27.73)	21.8 (18.53 to 30.88)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.464 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.861
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.577
upper limit	1.286

Notes:

[1] - Hazard Ratio (HR) was based on an unstratified Cox proportional hazard regression model with treatment as a factor. P-value is from an unstratified log-rank test.

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

EFS is defined as the time from the date of randomization to the date of the occurrence of an event. An event is defined as death or transformation to AML for HR MDS/CMML participants, whichever occurs first, or defined as death for low-blast AML participants. HR MDS/CMML participants without documented EFS event will be censored at the date of the last response assessment. HR MDS/CMML participants with no response assessment and no death will be censored at the date of randomization. Low-blast AML participants without documentation of death will be censored at the date the participant was last known to be alive. HR MDS/CMML participants who received alternative antineoplastic therapy before death or transformation to AML will be censored at the date of last adequate assessment prior to starting alternate antineoplastic therapy. The Kaplan-Meier estimate was used for the analysis. ITT Population was defined as all participants who were randomized.

End point type	Secondary

End point timeframe:

From date of randomization until transformation to AML, or death due to any cause (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: months				
median (confidence interval 95%)	17.6 (11.96 to 20.50)	21.0 (17.41 to 28.02)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.706
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.469
upper limit	1.061

Notes:

[2] - P-value is based on the unstratified log-rank test. HR:unadjusted stratified Cox proportional hazard regression with treatment as factor.HR<1:better prevention of EFS in combination arm than azacitidine arm.

Secondary: Six-month Survival Rate

End point title	Six-month Survival Rate

End point description:

Six-month survival rate was defined as the percentage of participants that survived at the end of the Month 6 from randomization. Percentage of participants was based on Kaplan-Meier estimate of probability. ITT Population was defined as all participants who were randomized. Overall number analyzed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Month 6

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percentage of participants				
number (confidence interval 95%)	0.806 (0.684 to 0.885)	0.914 (0.805 to 0.963)		

Statistical analyses

No statistical analyses for this end point

Secondary: One-year Survival Rate

End point title	One-year Survival Rate

End point description:

One-year survival rate was defined as the percentage of participants that survived at the end of the first year from randomization. Percentage of participants was based on Kaplan-Meier estimate of probability. ITT Population was defined as all participants who were randomized. Overall number analyzed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Month 12

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	49		
Units: percentage of participants				
number (confidence interval 95%)	0.677 (0.546 to 0.778)	0.845 (0.723 to 0.916)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to AML Transformation in HR MDS or CMML Participants

End point title	Time to AML Transformation in HR MDS or CMML Participants

End point description:

Time to AML transformation in HR MDS and CMML participants is defined as time from randomization to documented AML transformation. Participants without documented AML transformation at the time of the analysis are censored at the date of the last assessment. Participants who died before progression to AML are censored at the date of death. Transformation to AML is defined, according to World Health Organization (WHO) classification, as a participant having >20% blasts in the blood or marrow and increase of blast count by 50%. ITT Population was defined as all participants who were randomized. Overall number of participants analyzed is the number of participants with data available for analyses. 999= The median, lower limit and upper limit of 95% confidence interval (CI) was not estimable due to lower number of participants with the event.

End point type	Secondary

End point timeframe:

From date of randomization until transformation to AML (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	41		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.267 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.562
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.579

Notes:

[3] - P-value is from an unstratified log-rank test. Hazard ratio (HR) is based on an unstratified Cox proportional hazard regression model with treatment as a factor.

Secondary: Percentage of Participants With Complete Remission (CR)

End point title	Percentage of Participants With Complete Remission (CR)

End point description:

Disease responses for HR MDS or CMML=based on the modified International Working Group (IWG) response criteria for MDS and for low-blast AML on the revised IWG response criteria for AML.CR for HR MDS or CMML:≤5% myeloblasts with normal maturation of all cell lines in the bone marrow ≥11 gram/deciliter (g/dL) hemoglobin (Hb), ≥100*10^9/liter (/L) platelets (plt), ≥1.0*10^9/L absolute neutrophil count (ANC) and 0% blasts in peripheral blood.CR for low-blast AML: morphologic leukemia-free state,ANC of more than 1.0*10^9/L and plt of ≥1.0*10^9/L,transfusion independence,and no residual evidence of extramedullary leukemia.CR with incomplete blood count recovery for low-blast AML:some participants fulfill all of the criteria for CR except for residual neutropenia (<1.0*10^9/L) or thrombocytopenia (TTP)(<100*10^9/L).Response-Evaluable Population (REP) included all participants who received at least 1 dose of study drug and had a Baseline and at least 1 postbaseline disease assessment.

End point type	Secondary

End point timeframe:

From date of randomization until CR (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: percentage of participants				
number (not applicable)	36	45		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	9.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.83
upper limit	28.04

Notes:

[4] - P-value is from an unstratified Cochran-Mantel Haenszel chi-square test. Absolute difference >0 represent better response achieved on pevonedistat combination compared to azacitidine treatment alone.

Secondary: Percentage of Participants With CR and Partial Remission (PR)

End point title	Percentage of Participants With CR and Partial Remission (PR)

End point description:

Disease responses for HR MDS/CMML per modified IWG response criteria for MDS and for low-blast AML on revised IWG response criteria for AML.CR for HR MDS/CMML:≤5% myeloblasts with normal maturation of all cell lines in bone marrow, ≥11 g/dL Hb; ≥100*10^9/L plt; ≥1.0*10^9/L ANC and 0% blasts in peripheral blood. PR for HR MDS/CMML:considered achieved if all CR criteria is met except for bone marrow blasts decreased by ≥50%over pretreatment but still >5%. CR for low-blast AML:morphologic leukemia-free state, ANC of >1.0*10^9/L and plt of≥100*10^9/L, transfusion independence, no residual evidence of extramedullary leukemia. CRi for low-blast AML:fulfill criteria for CR except for residual neutropenia (<100*10^9/L)/TTP(<100*10^9/L). PR for low-blast AML:all hematological values for CR but with decrease of ≥50% in percentage of blasts to 5%-25% in bone marrow aspirate. REP: all participants who received ≥1 dose of study drug, had Baseline and ≥1 postbaseline disease assessment.

End point type	Secondary

End point timeframe:

From date of randomization until CR and PR (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: percentage of participants				
number (not applicable)	45	51		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	5.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.19
upper limit	24.44

Notes:

[5] - P-value is from an unstratified Cochran-Mantel Haenszel chi-square test. Absolute difference >0 represent better response achieved on pevonedistat combination compared to azacitidine treatment alone.

Secondary: Percentage of Participants With Overall Response

End point title	Percentage of Participants With Overall Response

End point description:

Disease responses (HR MDS/CMML): modified IWG criteria for MDS; low-blast (LB) AML: revised IWG criteria for AML. Overall response(HR MDS/CMML)=CR,PR/HI,LB AML=CR+ CR with Cri+PR.HR MDS/CMML-CR:≤5%myeloblasts with normal maturation of bone marrow (BM) cell lines,≥11g/dL Hb,≥100*10^9/L plt,≥1.0*10^9/L ANC,0% blasts in peripheral blood; PR:CR criteria met except BM blasts≥50%less over pretreatment but still>5%; HI:hb increase (inc)≥1.5g/dL if baseline<11g/dL;plt inc≥30*10^9/L if baseline>20*10^9/L/Inc. from <20*10^9/L->20*10^9/L, ANC inc. by 100%;absolute inc. of>0.5*10^9/L if baseline<100*10^9/L. LB AML-CR:morphologic leukemia-freestate>1.0*10^9ANC, ≥100*10^9/L plt, transfusion independence, no residual evidence of extramedullary leukemia;CRi:fulfill CR criteria except residual neutropenia<1.0*10^9/L/TTP<100*10^9/L;PR:all CR hematological values but≥50%less in BM aspirate. REP: all participants who received ≥1 dose of study drug, had Baseline and ≥1 postbaseline

End point type	Secondary

End point timeframe:

From date of randomization until CR, PR, or hematologic improvement (HI) (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: percentage of participants				
number (not applicable)	62	71		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.343 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	8.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.09
upper limit	26.38

Notes:

[6] - P-value was obtained from a stratified Cochran-Mantel-Haenszel chi-square test stratified by low-blast AML. Absolute difference >0 represent better response achieved on pevonedistat combination compared to azacitidine treatment alone.

Secondary: Percentage of Participants With CR in low-blast AML

End point title	Percentage of Participants With CR in low-blast AML

End point description:

Disease response for low-blast AML is based on the revised IWG response criteria for AML. CR for low-blast AML: morphologic leukemia-free state, ANC of more than 1.0*10^9/L and plt of >=1.0*10^9/L, transfusion independence, and no residual evidence of extramedullary leukemia. CR with incomplete blood count recovery for low-blast AML: some participants fulfill all of the criteria for CR except for residual neutropenia (<1.0*10^9/L) or thrombocytopenia (TTP) (<100*10^9/L). REP included all participants who received at least 1 dose of study drug and had a Baseline and at least 1 postbaseline disease assessment. Overall number analyzed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

From date of randomization until CR (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: percentage of participants				
number (not applicable)	60.0	41.2		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.296 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-18.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.91
upper limit	15.26

Notes:

[7] - P-value is from an unstratified Cochran-Mantel-Haenszel chi-square test. Absolute difference >0 represent better response achieved on pevonedistat combination compared to azacitidine treatment alone.

Secondary: Percentage of Participants With CR by Cycle 4

End point title	Percentage of Participants With CR by Cycle 4

End point description:

Disease responses for HR MDS or CMML were based on modified IWG response criteria for MDS and for low-blast AML on revised IWG response criteria for AML. CR for HR MDS or CMML: <=5% myeloblasts with normal maturation of all cell lines in bone marrow, and >=11 g/dL Hb, >=100*10^9/L plt, ANC >=1.0*10^9/L and 0% blasts in peripheral blood. CR for low-blast AML: morphologic leukemia-free state, ANC of more than 1.0*10^9/L and plt of >=100*10^9/L, transfusion independence, no residual evidence of extramedullary leukemia. CR with incomplete blood count recovery for low-blast AML: some participants fulfill all criteria for CR except for residual neutropenia (<1.0*10^9/L)/TTP (<100*10^9/L). REP included all participants who received at least 1 dose of study drug and had a Baseline and at least 1 postbaseline disease assessment. Overall number (N) analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

From date of randomization until CR by Cycle 4 (cycle length is equal to [=] 28 days)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: percentage of participants				
number (not applicable)	13.2	26.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.152 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	13.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	30.81

Notes:

[8] - P-value is from an unstratified Cochran-Mantel Haenszel chi-square test. Absolute difference >0 represent better response achieved on pevonedistat combination compared to azacitidine treatment alone.

Secondary: Percentage of Participants With CR and PR by Cycle 4

End point title	Percentage of Participants With CR and PR by Cycle 4

End point description:

Disease responses for HR MDS/CMML per modified IWG response criteria for MDS and for low-blast AML on revised IWG response criteria for AML.CR for HR MDS/CMML:≤5% myeloblasts with normal maturation of all cell lines in BM,≥11 g/dL Hb;≥100*10^9/L plt;≥1.0*10^9/L ANC and 0% blasts in peripheral blood.PR for HR MDS/CMML:achieved if all CR criteria is met except for BM blasts decreased by≥50% over pretreatment but still>5%.CR for low-blast AML:morphologic leukemia-free state,ANC of>1.0*10^9/L and plt of≥100*10^9/L,transfusion independence,no residual evidence of extramedullary leukemia.CRi for low-blast AML:fulfill all criteria for CR except for residual neutropenia (<100*10^9/L)/TTP (<100*10^9/L).PR for low-blast AML:all hematological values for CR but with decrease of ≥50% in percentage of blasts to 5%-25% in BM aspirate.REP:all participants who received ≥1 dose of study drug,had Baseline and ≥1 postbaseline disease assessment.N=number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

From date of randomization until CR and PR, by Cycle 4 (cycle length=28 days)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: percentage of participants				
number (not applicable)	21.1	31.6		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.301 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	10.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.13
upper limit	30.18

Notes:

[9] - P-value is from an unstratified Cochran-Mantel Haenszel chi-square test. Absolute difference >0 represent better response achieved on pevonedistat combination compared to azacitidine treatment alone.

Secondary: Percentage of Participants With Overall Response by Cycle 4

End point title	Percentage of Participants With Overall Response by Cycle 4

End point description:

Disease responses (HR MDS/CMML): modified IWG criteria for MDS;LB AML:revised IWG criteria for AML.Overall response(HR MDS/CMML)=CR,PR/HI,LB AML=CR+ CR with Cri+PR.HR MDS/CMML-CR:≤5%myeloblasts with normal maturation of BM cell lines,≥11g/dL Hb,≥100*10^9/L plt,≥1.0*10^9/L ANC,0% blasts in peripheral blood;PR:CR criteria met except BM blasts≥50%less over pretreatment but still>5%; HI:hb inc≥1.5g/dL if baseline<11g/dL;plt inc≥30*10^9/L if baseline>20*10^9/L/Inc. from <20*10^9/L->20*10^9/L,ANC inc. by 100%;absolute inc. of>0.5*10^9/L if baseline<100*10^9/L.LB AML-CR:morphologic leukemia-freestate>1.0*10^9ANC,≥100*10^9/L plt,transfusion independence,no residual evidence of extramedullary leukemia;CRi:fulfill CR criteria except residual neutropenia<1.0*10^9/L/TTP<100*10^9/L;PR:all CR hematological values but≥50%less in BM

End point type	Secondary

End point timeframe:

From date of randomization until CR, PR or HI, by Cycle 4 (cycle length=28 days)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: percentage of participants				
number (not applicable)	44.7	57.9		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.254 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	13.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.12
upper limit	35.44

Notes:

[10] - P-value is from an unstratified Cochran-Mantel Haenszel chi-square test. Absolute difference >0 represent better response achieved on pevonedistat combination compared to azacitidine treatment alone.

Secondary: Percentage of Participants With CR in low-blast AML by Cycle 4

End point title	Percentage of Participants With CR in low-blast AML by Cycle 4

End point description:

Disease response for low-blast AML is based on revised IWG response criteria for AML. CR for low-blast AML: morphologic leukemia-free state, ANC of more than 1.0*10^9/L and ptl of >=100*10^9/L, transfusion independence, no residual evidence of extramedullary leukemia. CR with incomplete blood count recovery for low-blast AML: some participants fulfill all criteria for CR except for residual neutropenia (<1.0*10^9/L)/TTP (<100*10^9/L). REP included all participants who received at least 1 dose of study drug and had a Baseline and at least 1 postbaseline disease assessment. Data is reported for low blast AML participants which is included as the overall number of participants analyzed.

End point type	Secondary

End point timeframe:

From the date of randomization until CR by Cycle 4 (cycle length=28 days)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: percentage of participants				
number (not applicable)	40.0	35.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.787 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-4.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.33
upper limit	28.92

Notes:

[11] - P-value is from an unstratified Cochran-Mantel Haenszel chi-square test. Absolute difference >0 represent better response achieved on pevonedistat combination compared to azacitidine treatment alone.

Secondary: Duration of Complete Remission (CR)

End point title	Duration of Complete Remission (CR)

End point description:

Duration of CR is first documented CR to the first documentation of PD or relapse from CR (participants with low-blast AML) or relapse after CR or PR (participants with HR MDS/CMML). Disease responses for HR MDS or CMML are based on the Modified IWG Response Criteria for MDS and for low-blast AML on the Revised IWG Response Criteria for AML.CR for HR MDS or CMML≤5% myeloblasts with normal maturation of all cell lines in the bone marrow,≥11 g/dL Hgb,≥100*10^9/L pl,≥1.0*10^9/L neutrophils;0% blasts in peripheral blood.CR for low-blast AML:morphologic leukemia-free state,neutrophils of<1.0*10^9/L;pl of≥100*10^9/L,transfusion independence,no residual evidence of extramedullary leukemia.CRi for low-blast AML: participants fulfill all of the criteria for CR except for residual neutropenia (<1.0*10^9/L) or thrombocytopenia (pl<100*10^9/L). REP was analysed.N=complete responders.999=upper limit of full range was not estimable due to lower number of participants with event.

End point type	Secondary

End point timeframe:

From date of randomization until CR (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	25		
Units: months				
median (full range (min-max))	12.9 (8.31 to 999)	18.6 (9.00 to 999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.789
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.308
upper limit	2.02

Notes:

[12] - P-value is from an unstratified log-rank test. Hazard ratio was based on an unstratified Cox proportional hazard regression model and treatment as a factor in the model.

Secondary: Duration of Complete Remission (CR) and Partial Remission (PR)

End point title	Duration of Complete Remission (CR) and Partial Remission (PR)

End point description:

Duration of CR=first documented CR to the first documentation of PD or relapse from CR (participants with low-blast AML).Disease responses (HR MDS/CMML) are based on modified IWG response criteria for MDS and for low-blast AML on revised IWG response criteria for AML.For HR MDS/CMML-CR:≤5%myeloblasts with normal maturation of all BM cell lines,≥11 g/dL Hb,≥100*10^9/L plt,≥1.0*10^9/L neutrophils,0% blasts in peripheral blood;PR:all CR criteria met except BM blasts ≥50% decrease over pretreatment but still >5%;low-blast AML-CR:morphologic leukemia-free state,>1.0*10^9/L ANC,plt ≥100*10^9/L,transfusion independence,no residual evidence of extramedullary leukemia;CRi:fulfill CR criteria except residual neutropenia <1.0*10^9/L/TTP <100*10^9/L;PR:all CR hematological values but with a decrease of ≥50% in blasts percentage to 5%-25% in bone marrow aspirate. REP was analysed.N=CR and PR responders. 999=Upper limit of full range was not estimable due to lower number of participants with event.

End point type	Secondary

End point timeframe:

From date of randomization until CR or PR (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	28		
Units: months				
median (confidence interval 95%)	12.9 (8.31 to 999)	18.6 (10.15 to 999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.436 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.719
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.313
upper limit	1.653

Notes:

[13] - P-value is from an unstratified log-rank test. Hazard ratio was based on an unstratified Cox proportional hazard regression model and treatment as a factor in the model.

Secondary: Duration of Overall Response

End point title	Duration of Overall Response

End point description:

OR Duration:Response(RE)to first documentation of PD/relapse(RS)fromCR for low-blast(LB)AML/RS afterCR/PR forHRMDS/CMML.Disease REs(HRMDS/CMML):modifiedIWG criteria(CA) forMDS;LBAML:revisedIWG CA forAML.Overall RE(HRMDS/CMML)=CR,PR/HI,LB AML=CR+CR Cri+PR.HRMDS/CMML-CR:≤5%myeloblasts withBMcell lines' normal maturation,≥11g/dL Hb,≥100*10^9/L plt,≥1.0*10^9/L ANC,0%blasts(bs) in peripheral blood;PR:CR CA met except BM bs≥50%less over pretreatment,still>5%; HI:hb increase(IE)≥1.5g/dL if baseline(BL)<11g/dL;plt IE≥30*10^9/L if BL>20*10^9/L IEfrom<20*10^9/L->20*10^9/L,ANC IEby100%;absoluteIE>0.5*10^9/L ifBL<100*10^9/L.LBAML-CR:MorphologicLeukemia(LA)-freestate>1.0*10^9 ANC,≥100*1^9/Lplt,transfusion independence,no extramedullaryLA residual(RL)evidence;CRi:fulfil CR CAexcept RLneutropenia<1.0*10^9/L/TTP<100*10^9/L;PR:all CR HematologicValues,≥50%less in BM aspirate.SubjectsAnalyzed=REP responders.999=full range

End point type	Secondary

End point timeframe:

From date of randomization until CR, PR or HI (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: months				
median (full range (min-max))	14.0 (12.62 to 999)	20.6 (10.71 to 999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.565 [14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.395
upper limit	1.662

Notes:

[14] - P-value is from an unstratified log-rank test. Hazard ratio was based on an unstratified Cox proportional hazard regression model and treatment as a factor in the model.

Secondary: Duration of Complete Remission (CR) in Low-blast AML

End point title	Duration of Complete Remission (CR) in Low-blast AML

End point description:

Disease responses for low-blast AML is based on revised IWG response criteria for AML. CR for low-blast AML: morphologic leukemia-free state, ANC of more than 1.0*10^9/L and plt of >=100*10^9/L, transfusion independence, no residual evidence of extramedullary leukemia. CR with incomplete blood count recovery for low-blast AML: some participants fulfill all criteria for CR except for residual neutropenia (<1.0*10^9/L)/TTP (<100*10^9/L). REP included all participants who received at least 1 dose of study drug and had a Baseline and at least 1 postbaseline disease assessment. Data is reported for AML participants which is included as the overall number of participants analyzed.

End point type	Secondary

End point timeframe:

From date of randomization until CR (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: months				
median (full range (min-max))	10.2 (0.2 to 10.2)	12.6 (5.6 to 44.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.383 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	3.109

Notes:

[15] - P-value is from an unstratified log-rank test. Hazard ratio was based on an unstratified Cox proportional hazard regression model and treatment as a factor in the model.

Secondary: Time to First CR or PR

End point title	Time to First CR or PR

End point description:

Time to first CR or PR: time from randomization to first documented CR or PR, whichever occurs first. Disease responses (HR MDS/CMML) based on modified IWG response criteria for MDS; low-blast AML on revised IWG response criteria for AML. HR MDS/CMML-CR:≤5% myeloblasts with normal maturation of all BM cell lines,≥11 g/dL Hb,≥100*10^9/L plt,≥1.0*10^9/L ANC,0% blasts in peripheral blood;PR: all CR criteria met except BM blasts ≥50% decrease over pretreatment but still >5%;For low-blast AML-CR:morphologic leukemia-free state,>1.0*10^9/L ANC, plt ≥100*10^9/L, transfusion independence,no residual evidence of extramedullary leukemia;CR with incomplete blood count recovery:fulfill CR criteria except residual neutropenia <1.0*10^9/L/TTP <100*10^9/L; PR:all CR hematological values but with a decrease of ≥50% in the percentage of blasts to 5% to 25% in the BM aspirate.REP was analysed.999=Upper limit of 95% CI was not estimable due to lower number of participants with event.

End point type	Secondary

End point timeframe:

From date of randomization until CR or PR (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: months				
median (confidence interval 95%)	13.2 (6.4 to 999)	8.3 (4.5 to 999)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.498 [17]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.206
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.699
upper limit	2.081

Notes:

[16] - HR is based on an unstratified Cox proportional hazard regression model with treatment as a factor. HR>1 for the treatment indicates a shorter time to first CR, CRi or PR in the Pevonedistat Combination arm compared to the Azacitidine only arm.

[17] - P-value is from an unstratified log-rank test.

Secondary: Time to Subsequent Therapy

End point title	Time to Subsequent Therapy

End point description:

Time to subsequent therapy is defined as time from randomization to the date of the first subsequent therapy. Subsequent therapy is defined as agent(s) with antileukemic/anti-MDS activity. Participants who discontinue study treatment to receive single-agent azacitidine off study did not be counted as receiving subsequent therapy. ITT Population was defined as all participants who were randomized. 999=The median, lower limit and upper limit of 95% CI was not estimable due to lower number of participants with the event.

End point type	Secondary

End point timeframe:

From date of randomization up to approximately 5 years

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

HR is based on an unstratified Cox proportional hazard regression model with treatment as a factor. HR>1 for the treatment indicates a shorter time to first CR, CRi or PR in the Pevonedistat Combination arm compared to the Azacitidine only arm.

Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.888 [18]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.905
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.226
upper limit	3.62

Notes:

[18] - P-value is from an unstratified log-rank test.

Secondary: Percentage of Participants With Red Blood Cells (RBCs) and Platelet-transfusion Independence

End point title	Percentage of Participants With Red Blood Cells (RBCs) and Platelet-transfusion Independence

End point description:

A participant was defined as RBC or platelet-transfusion independent if he/she received no RBC or platelet transfusions for a period of at least 8 weeks before the first dose of study drug through 30 days after the last dose of any study drug. Rate of transfusion independence was defined as number of participants who became transfusion independent divided by the number of participants who were transfusion dependent at Baseline. ITT Population included all participants who were randomized. Overall number analyzed are the number of participants from a subset of the ITT Population who were transfusion dependent at Baseline. Number analyzed is the number of participants who were transfusion dependent at Baseline for the specified category.

End point type	Secondary

End point timeframe:

8 weeks before randomization through 30 days after last dose of any study drug (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: percentage of participants				
number (not applicable)				
RBCs-transfusion Independence(n=26,26)	50.0	69.2		
Platelet-transfusion Independence(n=10,5)	60.0	80.0		

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:	
Percentage of Participants With Platelet-transfusion Independence	
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.454 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.381
upper limit	66.381

Notes:

[19] - P-value is from an unstratified Cochran-Mantel Haenszel chi-square test.

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Percentage of Participants With RBCs-transfusion Independence	
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	19.231
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.925
upper limit	45.386

Notes:

[20] - P-value is from an unstratified Cochran-Mantel Haenszel chi-square test.

Secondary: Percentage of Participants With at least 1 Inpatient Hospital Admissions Related to HR MDS, CMML or Low-blast AML

End point title	Percentage of Participants With at least 1 Inpatient Hospital Admissions Related to HR MDS, CMML or Low-blast AML

End point description:

Inpatient hospital admission data was collected through transformation to AML (HR MDS/CMML participants) or disease progression (low-blast AML participants) or until initiation of subsequent therapy (all participants), whichever occurred first. Transformation to AML is defined, according to WHO Classification, as a participant having 20% blasts in the blood or marrow and increase of blast count by 50%. Percentage of participants was calculated as the total number of events divided by the total number of subject-years in each group. ITT Population included all participants who were randomized.

End point type	Secondary

End point timeframe:

From date of randomization until transformation to AML or until initiation of subsequent therapy (up to

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: percentage of participants				
number (confidence interval 95%)	0.4811 (0.37956 to 0.58265)	0.5878 (0.42606 to 0.74953)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progressive Disease (PD), Relapse, or Death

End point title	Time to Progressive Disease (PD), Relapse, or Death

End point description:

Time from randomization until PD/transformation to AML/relapse/death due to any cause, whichever occurs first. Relapse after CR or PR in MDS/CMML: return to pretreatment bone marrow blast % or decrement of >=50% from maximum remission levels in ANC or plt, reduction in Hb concentration by >=1.5 g/dL or transfusion dependence. PD: at least 50% decrement from maximum remission in ANC or plt, or reduction in Hb by>=2g/dL or transfusion dependence;participants with <5% blasts: >=50% increase (inc) in blasts to >5%; 5%-10%: >=50% inc to >10%; 10%-20%: >=50% inc to>20%;20%-30%:>=50% inc to >30%. Relapse after CR in Low blast AML: reappearance of leukemic blasts in peripheral blood or >=5% blasts in bone marrow not attributable to any cause (example, bone marrow regeneration after consolidation therapy). If there are no circulating blasts, bone marrow contains 5%-20% blasts, a repeat analysis is performed a week later. ITT Population was defined as all participants who were randomized.

End point type	Secondary

End point timeframe:

From date of randomization until PD, relapse or death (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: months				
median (full range (min-max))	13.6 (9.40 to 16.53)	15.2 (12.39 to 20.83)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.266 [22]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.521
upper limit	1.198

Notes:

[21] - HR is based on an unstratified Cox proportional hazard regression model with treatment as a factor. A HR<1for the treatment indicates a better prevention of PD, relapse after CR or PR, or death in the Pevonedistat Combination arm compared to the Azacitidine only arm.
[22] - P-value is from an unstratified log-rank test.

Secondary: Number of Participants Reporting one or More Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants Reporting one or More Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

Adverse event=any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.SAE=any untoward medical occurrence that:results in death;is life-threatening;requires inpatient hospitalization or prolongation of existing hospitalization;results in persistent or significant disability/incapacity;leads to a congenital anomaly/birth defect in the offspring of the participant or is a medically important event that satisfies any of the following:a) May require intervention to prevent items 1 through 5 above.b) May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.TEAE=any adverse event occurring after the start of pevonedistat administration of the treatment period.Safety Population=all enrolled participants who receive at least 1 dose of any study drug azacitidine alone or pevonedistat + azacitidine.

End point type	Secondary

End point timeframe:

From date of randomization up to 30 days after administration of the last dose of any study drug (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: participants				
TEAEs	62	57		
SAEs	40	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants in the Safety Analysis Population With Clinically Significant Laboratory Abnormalities Reported as TEAEs

End point title	Number of Participants in the Safety Analysis Population With Clinically Significant Laboratory Abnormalities Reported as TEAEs

End point description:

Laboratory assessments included clinical chemistry, hematology, and urinalysis. Safety Population included all enrolled participants who receive at least 1 dose of any study drug azacitidine alone or pevonedistat + azacitidine.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after administration of the last dose of any study drug (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: participants				
Neutropenia	21	21		
Anaemia	29	19		
Neutrophil count decreased	6	12		
Thrombocytopenia	15	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Change From Baseline Values in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Number of Participants With Change From Baseline Values in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point description:

Number of participants with change from Baseline in ECOG performance status was measured on 6 point scale to assess participant's performance status, where: Grade 0(Normal activity. Fully active, able to carry on all pre-disease activities without restriction); Grade 1(Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out light or sedentary work); Grade 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); Grade 3(In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50 percent of waking hours); Grade 4(100% bedridden. Completely disabled, cannot carry on any self-care, totally confined to bed or chair); Grade 5(Dead). ITT population=all participants who were randomized in the Safety Population. Only categories for which there was at least 1 participant are reported.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after administration of the last dose of any study drug (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: participants				
Baseline: 0; Overall: 0	13	9		
Baseline: 0; Overall: 1	15	13		
Baseline: 0; Overall: 2	3	3		
Baseline: 0; Overall: 3	0	2		
Baseline: 0; Overall: 4	2	0		
Baseline: 1; Overall: 1	17	18		
Baseline: 1; Overall: 2	5	8		
Baseline: 1; Overall: 3	5	2		
Baseline: 2; Overall: 2	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants in the Safety Analysis Population With Clinically Significant Change From Baseline in Electrocardiogram (ECG) Values Reported as TEAEs

End point title	Number of Participants in the Safety Analysis Population With Clinically Significant Change From Baseline in Electrocardiogram (ECG) Values Reported as TEAEs

End point description:

ECG assessments included QT, QRS duration, PR interval, ventricular rate, QTcB, QTcF. Safety Population included all enrolled participants who receive at least 1 dose of any study drug azacitidine alone or pevonedistat + azacitidine.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after administration of the last dose of any study drug (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: participants				
Atrial fibrillation	4	4		
Tachycardia	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants in the Safety Analysis Population With Clinically Significant Change From Baseline Values in Vital Signs Reported as TEAEs

End point title	Number of Participants in the Safety Analysis Population With Clinically Significant Change From Baseline Values in Vital Signs Reported as TEAEs

End point description:

Vital signs assessments included diastolic and systolic blood pressure, heart rate, and body temperature. Safety Population included all enrolled participants who receive at least 1 dose of any study drug azacitidine alone or pevonedistat + azacitidine.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after administration of the last dose of any study drug (up to approximately 5 years)

End point values	Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: participants				
Pyrexia	25	22		
Hypotension	3	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days after administration of the last dose of any study drug (up to approximately 5 years)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events, abnormal laboratory findings, and vital signs. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2

Reporting group description:

Azacitidine 75 mg/m^2, infusion, intravenously or subcutaneously, on Day 1 through Day 5, Days 8 and 9 and pevonedistat 20 mg/m^2, infusion, intravenously, on Days 1, 3, and 5 in 28-day treatment cycles until unacceptable toxicity, relapse, transformation to AML (for participants with HR MDS or CMML), or progressive disease (for participants with low-blast AML).

Reporting group title	Azacitidine 75 mg/m^2

Reporting group description:

Azacitidine 75 mg/m^2, infusion, intravenously or subcutaneously, on Day 1 through Day 5, Days 8 and 9 in 28-day treatment cycles until unacceptable toxicity, relapse, transformation to AML (for participants with HR MDS or CMML), or progressive disease (for participants with low-blast AML).

Serious adverse events	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2	Azacitidine 75 mg/m^2	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 58 (68.97%)	40 / 62 (64.52%)	
number of deaths (all causes)	47	50	
number of deaths resulting from adverse events	8	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified recurrent			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myelodysplastic syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myelodysplastic syndrome transformation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthenia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 58 (5.17%)	6 / 62 (9.68%)	
occurrences causally related to treatment / all	0 / 3	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infiltration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	2 / 58 (3.45%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Post procedural hypotension			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 58 (3.45%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Embolic stroke			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 58 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	13 / 58 (22.41%)	15 / 62 (24.19%)	
occurrences causally related to treatment / all	6 / 20	8 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Parophthalmia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 58 (3.45%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 58 (3.45%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer perforation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastritis erosive			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic gastritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 58 (3.45%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	2 / 58 (3.45%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	2 / 58 (3.45%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 58 (3.45%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral viral infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	2 / 58 (3.45%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronavirus infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	8 / 58 (13.79%)	7 / 62 (11.29%)	
occurrences causally related to treatment / all	2 / 12	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pseudomonas infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory syncytial virus bronchiolitis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 58 (6.90%)	4 / 62 (6.45%)	
occurrences causally related to treatment / all	1 / 4	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 58 (3.45%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2	Azacitidine 75 mg/m^2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 58 (87.93%)	58 / 62 (93.55%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	7 / 58 (12.07%)	0 / 62 (0.00%)	
occurrences (all)	11	0	
Hypotension			
subjects affected / exposed	6 / 58 (10.34%)	0 / 62 (0.00%)	
occurrences (all)	7	0	
Hypertension			

subjects affected / exposed	4 / 58 (6.90%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Pallor			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	4 / 58 (6.90%)	7 / 62 (11.29%)	
occurrences (all)	5	7	
Fatigue			
subjects affected / exposed	12 / 58 (20.69%)	25 / 62 (40.32%)	
occurrences (all)	20	33	
Chills			
subjects affected / exposed	4 / 58 (6.90%)	7 / 62 (11.29%)	
occurrences (all)	4	7	
Asthenia			
subjects affected / exposed	18 / 58 (31.03%)	13 / 62 (20.97%)	
occurrences (all)	28	20	
Injection site reaction			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Malaise			
subjects affected / exposed	0 / 58 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Non-cardiac chest pain			
subjects affected / exposed	0 / 58 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	6	
Oedema peripheral			
subjects affected / exposed	12 / 58 (20.69%)	9 / 62 (14.52%)	
occurrences (all)	17	12	
Pyrexia			
subjects affected / exposed	21 / 58 (36.21%)	22 / 62 (35.48%)	
occurrences (all)	36	34	
Peripheral swelling			

subjects affected / exposed	5 / 58 (8.62%)	0 / 62 (0.00%)	
occurrences (all)	6	0	
Pain			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 58 (37.93%)	21 / 62 (33.87%)	
occurrences (all)	31	25	
Productive cough			
subjects affected / exposed	6 / 58 (10.34%)	4 / 62 (6.45%)	
occurrences (all)	7	5	
Pleural effusion			
subjects affected / exposed	0 / 58 (0.00%)	5 / 62 (8.06%)	
occurrences (all)	0	5	
Oropharyngeal pain			
subjects affected / exposed	4 / 58 (6.90%)	6 / 62 (9.68%)	
occurrences (all)	4	6	
Nasal congestion			
subjects affected / exposed	5 / 58 (8.62%)	4 / 62 (6.45%)	
occurrences (all)	5	5	
Epistaxis			
subjects affected / exposed	13 / 58 (22.41%)	6 / 62 (9.68%)	
occurrences (all)	27	7	
Dyspnoea			
subjects affected / exposed	13 / 58 (22.41%)	16 / 62 (25.81%)	
occurrences (all)	15	21	
Dyspnoea exertional			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 58 (10.34%)	7 / 62 (11.29%)	
occurrences (all)	6	8	
Depression			

subjects affected / exposed	4 / 58 (6.90%)	0 / 62 (0.00%)	
occurrences (all)	5	0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 58 (6.90%)	5 / 62 (8.06%)	
occurrences (all)	6	8	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 58 (6.90%)	4 / 62 (6.45%)	
occurrences (all)	7	8	
Blood bilirubin increased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	8	0	
Blood creatinine increased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Neutrophil count decreased			
subjects affected / exposed	12 / 58 (20.69%)	6 / 62 (9.68%)	
occurrences (all)	22	18	
Platelet count decreased			
subjects affected / exposed	7 / 58 (12.07%)	7 / 62 (11.29%)	
occurrences (all)	10	19	
Weight decreased			
subjects affected / exposed	5 / 58 (8.62%)	5 / 62 (8.06%)	
occurrences (all)	7	5	
White blood cell count decreased			
subjects affected / exposed	4 / 58 (6.90%)	6 / 62 (9.68%)	
occurrences (all)	12	11	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 58 (8.62%)	4 / 62 (6.45%)	
occurrences (all)	5	4	
Fall			

subjects affected / exposed	8 / 58 (13.79%)	6 / 62 (9.68%)	
occurrences (all)	11	6	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Tachycardia			
subjects affected / exposed	4 / 58 (6.90%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Somnolence			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Headache			
subjects affected / exposed	3 / 58 (5.17%)	8 / 62 (12.90%)	
occurrences (all)	4	10	
Dizziness			
subjects affected / exposed	8 / 58 (13.79%)	9 / 62 (14.52%)	
occurrences (all)	11	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	19 / 58 (32.76%)	27 / 62 (43.55%)	
occurrences (all)	38	51	
Thrombocytopenia			
subjects affected / exposed	15 / 58 (25.86%)	15 / 62 (24.19%)	
occurrences (all)	38	36	
Neutropenia			
subjects affected / exposed	21 / 58 (36.21%)	21 / 62 (33.87%)	
occurrences (all)	70	52	
Febrile neutropenia			
subjects affected / exposed	0 / 58 (0.00%)	5 / 62 (8.06%)	
occurrences (all)	0	7	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Eye disorders			

Conjunctival haemorrhage			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 58 (32.76%)	17 / 62 (27.42%)	
occurrences (all)	27	28	
Constipation			
subjects affected / exposed	21 / 58 (36.21%)	29 / 62 (46.77%)	
occurrences (all)	39	38	
Abdominal pain			
subjects affected / exposed	3 / 58 (5.17%)	10 / 62 (16.13%)	
occurrences (all)	5	12	
Stomatitis			
subjects affected / exposed	0 / 58 (0.00%)	5 / 62 (8.06%)	
occurrences (all)	0	5	
Nausea			
subjects affected / exposed	21 / 58 (36.21%)	28 / 62 (45.16%)	
occurrences (all)	35	39	
Haemorrhoids			
subjects affected / exposed	5 / 58 (8.62%)	0 / 62 (0.00%)	
occurrences (all)	6	0	
Vomiting			
subjects affected / exposed	14 / 58 (24.14%)	13 / 62 (20.97%)	
occurrences (all)	22	17	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	4 / 58 (6.90%)	5 / 62 (8.06%)	
occurrences (all)	5	6	
Rash maculo-papular			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Pruritus			
subjects affected / exposed	3 / 58 (5.17%)	8 / 62 (12.90%)	
occurrences (all)	3	8	
Petechiae			

subjects affected / exposed	0 / 58 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 58 (6.90%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Dysuria			
subjects affected / exposed	4 / 58 (6.90%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Haematuria			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 58 (0.00%)	5 / 62 (8.06%)	
occurrences (all)	0	6	
Muscle spasms			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	9 / 58 (15.52%)	8 / 62 (12.90%)	
occurrences (all)	11	9	
Arthralgia			
subjects affected / exposed	6 / 58 (10.34%)	12 / 62 (19.35%)	
occurrences (all)	7	15	
Musculoskeletal pain			
subjects affected / exposed	0 / 58 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Pain in extremity			
subjects affected / exposed	10 / 58 (17.24%)	4 / 62 (6.45%)	
occurrences (all)	12	5	
Myalgia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			

Oral herpes			
subjects affected / exposed	0 / 58 (0.00%)	6 / 62 (9.68%)	
occurrences (all)	0	7	
Oral candidiasis			
subjects affected / exposed	3 / 58 (5.17%)	4 / 62 (6.45%)	
occurrences (all)	3	4	
Nasopharyngitis			
subjects affected / exposed	7 / 58 (12.07%)	4 / 62 (6.45%)	
occurrences (all)	10	4	
Bronchitis			
subjects affected / exposed	0 / 58 (0.00%)	7 / 62 (11.29%)	
occurrences (all)	0	7	
Pneumonia			
subjects affected / exposed	3 / 58 (5.17%)	8 / 62 (12.90%)	
occurrences (all)	3	8	
Urinary tract infection			
subjects affected / exposed	5 / 58 (8.62%)	5 / 62 (8.06%)	
occurrences (all)	10	17	
Respiratory tract infection			
subjects affected / exposed	3 / 58 (5.17%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 58 (18.97%)	13 / 62 (20.97%)	
occurrences (all)	12	17	
Dehydration			
subjects affected / exposed	0 / 58 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	5	
Hyperkalaemia			
subjects affected / exposed	4 / 58 (6.90%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 58 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	10	
Hypocalcaemia			

subjects affected / exposed	4 / 58 (6.90%)	4 / 62 (6.45%)	
occurrences (all)	6	5	
Hyponatraemia			
subjects affected / exposed	4 / 58 (6.90%)	4 / 62 (6.45%)	
occurrences (all)	16	8	
Hypomagnesaemia			
subjects affected / exposed	3 / 58 (5.17%)	5 / 62 (8.06%)	
occurrences (all)	3	7	
Hypokalaemia			
subjects affected / exposed	4 / 58 (6.90%)	11 / 62 (17.74%)	
occurrences (all)	5	18	
Hypophosphataemia			
subjects affected / exposed	0 / 58 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2015	The following changes were made in amendment 1: Revise study population to include participants with low-blast acute myelogenous leukemia (AML). Revise the number of participants expected to be enrolled in the study. Clarify definition of progressive disease for participants with low-blast AML. Clarify timing of event-free survival (EFS) visit for participants with higher-risk MDS (HR MDS), chronic myelomonocytic leukemia (CMML), or AML. Revise primary endpoint to reflect the addition of participants with low-blast AML. Revise secondary endpoints to reflect the addition of participants with low-blast AML. Delete secondary endpoint regarding collection of pevonedistat plasma concentrations since this information is captured in a secondary objective. Update statistical methods section to revise hazard ratio calculations and confidence intervals along with the estimated number of EFS events required. Add description of analyses for secondary efficacy endpoints. Revise section on timing of interim analyses (IA).
13 September 2016	Clarify that relapse includes relapse from complete remission (CR) and partial remission (PR) for participants with MDS/CMML, and relapse from CR for participants with AML. Add cytogenetic CR as an exploratory objective and endpoint. Add evaluation of minimal residual disease in participants who achieve CR in Cycle 4 or Cycle 7 as an exploratory objective and endpoint. Add relapse after CR as a response criterion for AML. Add cytogenetic CR as a response criterion for AML.
16 November 2017	Realign the analysis of the primary objective and endpoint as related to the change in the definition of an event for participants with low-blast AML. Specify the change in the follow-up process for participants with low-blast AML. Specify the trigger initiating the timing of the overall survival final analysis and other factor(s) that might affect the duration of the study. Clarify that Kaplan-Meier estimates and CIs of 6-month and 1-year survival rates will be provided based on the intent-to-treat population.
27 July 2018	The following changes were made in amendment 4: Clarify definition of safety population for purposes of analysis. Specify changes in general methodology for analysis of efficacy. Specify analyses of primary efficacy endpoint OS. Clarify methodology for analysis of secondary efficacy endpoints, including those that are response-related. Clarify populations for analyses of health-related quality of life.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported