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

Summary

EudraCT number	2017-000318-40
Trial protocol	GB DE CZ ES FR BE IT
Global end of trial date	14 October 2024

Results information

Result version number	v1 (current)
This version publication date	26 October 2025
First version publication date	26 October 2025

Trial information

Trial identification

Sponsor protocol code	Pevonedistat-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03268954
WHO universal trial number (UTN)	U1111-1189-8055

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, MA, United States, 02421
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	14 October 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to determine whether the combination of pevonedistat and azacitidine improves event-free survival (EFS), when compared with single-agent azacitidine. (An event is defined as death or transformation to acute myeloid leukemia (AML) in participants with MDS or CMML, whichever occurs first, and is defined as death in participants with low-blast AML.)

Protection of trial subjects:

Participant signed an informed consent form (ICF) before participating in the study.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	28 November 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	38 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Brazil: 28
Country: Number of subjects enrolled	China: 2
Country: Number of subjects enrolled	Czechia: 16
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Greece: 58
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Japan: 38
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Russian Federation: 34

Country: Number of subjects enrolled	Türkiye: 10
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	United States: 89
Worldwide total number of subjects	454
EEA total number of subjects	208

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)	51
From 65 to 84 years	383
85 years and over	20

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 130 investigative sites globally from 28 November 2017 to 14 October 2024.

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	Not blinded

Arms

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

Arm description:

Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9, in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

Arm type	Experimental
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9, in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

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

Arm description:

Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9 and pevonedistat 20 mg/m^2 IV infusion, on Days 1, 3, and 5 in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

Arm type	Experimental
Investigational medicinal product name	Pevonedistat
Investigational medicinal product code	TAK-924
Other name	MLN4924
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pevonedistat 20 mg/m^2 IV infusion, on Days 1, 3, and 5 in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9, in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

Number of subjects in period 1	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Started	227	227
Safety Population	220	223
Completed	195	199
Not completed	32	28
Consent withdrawn by subject	27	17
Reason Not Specified	3	8
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Azacitidine 75 mg/m^2
Reporting group description:	
Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9, in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.	
Reporting group title	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Reporting group description:	
Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9 and pevonedistat 20 mg/m^2 IV infusion, on Days 1, 3, and 5 in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.	

Reporting group values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2	Total
Number of subjects	227	227	454
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	73.0	73.0	
standard deviation	± 8.22	± 7.65	-
Gender categorical Units: Subjects			
Male	142	132	274
Female	85	95	180
Ethnicity Units: Subjects			
Hispanic or Latino	26	31	57
Not Hispanic or Latino	188	189	377
Unknown or Not Reported	13	7	20
Race Units: Subjects			
American Indian or Alaska Native	2	4	6
Asian	20	31	51
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	3
White	189	180	369
More than one race	0	0	0
Unknown or Not Reported	15	10	25
Region of Enrollment Units: Subjects			
Australia	3	4	7
Belgium	8	3	11
Brazil	10	18	28
China	2	0	2

Czech Republic	10	6	16
Germany	6	3	9
Spain	26	23	49
France	13	8	21
United Kingdom	1	3	4
Greece	30	28	58
Israel	6	6	12
Italy	14	9	23
Japan	12	26	38
Korea, Republic of	4	2	6
Poland	11	10	21
Russia	22	12	34
Turkey	5	5	10
Canada	2	7	9
Mexico	2	5	7
United States	40	49	89
Height			
999 is a placeholder value for the data that is reported in other subject analysis set or arm group, due to difference in number of subjects analyzed.			
Units: centimeter (cm)			
arithmetic mean	999	999	
standard deviation	± 999	± 999	-
Weight			
999 is a placeholder value for the data that is reported in other subject analysis set or arm group, due to difference in number of subjects analyzed.			
Units: kilogram (kg)			
arithmetic mean	77.65	999	
standard deviation	± 16.143	± 999	-
Body Surface Area			
Body surface area is defined as [height (cm) × weight (kg) / 3600]^1/2. 999 is a placeholder value for the data that is reported in other subject analysis set or arm group, due to difference in number of subjects analyzed.			
Units: meter square (m^2)			
arithmetic mean	999	999	
standard deviation	± 999	± 999	-

Subject analysis sets

Subject analysis set title	Azacitidine 75 mg/m^2
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9, in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

Subject analysis set title	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9 and pevonedistat 20 mg/m^2 IV infusion, on Days 1, 3, and 5 in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

Subject analysis set title	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9

Reporting group values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects	225	223	226
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	0	0	0
standard deviation	±	±	±
Gender categorical Units: Subjects			
Male	0	0	0
Female	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	0	0	0
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	0	0	0
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Australia	0	0	0
Belgium	0	0	0
Brazil	0	0	0
China	0	0	0
Czech Republic	0	0	0
Germany	0	0	0
Spain	0	0	0
France	0	0	0
United Kingdom	0	0	0
Greece	0	0	0
Israel	0	0	0
Italy	0	0	0
Japan	0	0	0
Korea, Republic of	0	0	0
Poland	0	0	0
Russia	0	0	0
Turkey	0	0	0

Canada	0	0	0
Mexico	0	0	0
United States	0	0	0
Height			
999 is a placeholder value for the data that is reported in other subject analysis set or arm group, due to difference in number of subjects analyzed.			
Units: centimeter (cm)			
arithmetic mean	167.59	166.31	999
standard deviation	± 9.439	± 10.098	± 999
Weight			
999 is a placeholder value for the data that is reported in other subject analysis set or arm group, due to difference in number of subjects analyzed.			
Units: kilogram (kg)			
arithmetic mean	999	999	75.82
standard deviation	± 999	± 999	± 15.996
Body Surface Area			
Body surface area is defined as [height (cm) × weight (kg) / 3600]^1/2. 999 is a placeholder value for the data that is reported in other subject analysis set or arm group, due to difference in number of subjects analyzed.			
Units: meter square (m^2)			
arithmetic mean	1.89	1.86	999
standard deviation	± 0.228	± 0.233	± 999

End points

End points reporting groups

Reporting group title	Azacitidine 75 mg/m^2
Reporting group description:	
Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9, in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.	
Reporting group title	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Reporting group description:	
Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9 and pevonedistat 20 mg/m^2 IV infusion, on Days 1, 3, and 5 in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.	
Subject analysis set title	Azacitidine 75 mg/m^2
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9, in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.	
Subject analysis set title	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9 and pevonedistat 20 mg/m^2 IV infusion, on Days 1, 3, and 5 in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.	
Subject analysis set title	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9 and pevonedistat 20 mg/m^2 IV infusion, on Days 1, 3, and 5 in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.	

Primary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)
End point description:	
EFS was defined as the time from randomization to the date of an EFS event. An EFS event was defined as death or transformation to acute myelogenous leukemia (AML) (World Health Organization [WHO] classification as a participant having greater than 20 % blasts in the blood or marrow and an increase of blast count by 50%), whichever event occurred first, in participants with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemias (CMML). An EFS event was defined as death in participants with low-blast AML. Intent-to-Treat (ITT) population included all participants who were randomized.	
End point type	Primary
End point timeframe:	
From randomization until transformation to acute myeloid leukemia, or death due to any cause: up to approximately 42 months	

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: months				
median (confidence interval 95%)	15.7 (14.42 to 19.68)	17.7 (13.63 to 20.24)		

Statistical analyses

Statistical analysis title	Event-Free Survival (EFS)
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.557 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.968
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.757
upper limit	1.238

Notes:

[1] - HR:unadjusted stratified Cox proportional hazard regression with stratification(low-blast AML, Revised International Prognostic Scoring System (IPSS-R) risk groups=very high,high,or intermediate for higher-risk (HR)MDS/CMML),treatment as factor.HR<1:better prevention of EFS in combination arm than azacitidine arm.

[2] - P-value comparing EFS between treatment groups was based on the 1-sided Cui-Hung-Wang weighted unstratified log-rank test.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time from randomization to death from any cause. ITT Population included all participants who were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 6.9 years

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: months				
median (confidence interval 95%)	16.8 (14.92 to 20.11)	20.3 (17.97 to 22.60)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.152 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.888
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.709
upper limit	1.113

Notes:

[3] - HR:unadjusted stratified Cox proportional hazard regression with stratification(low-blast AML,IPSS-R risk groups=very high,high,or intermediate for HRMDS/CMML),treatment as factor.HR<1: longer survival time in combination arm than azacitidine arm.

[4] - P-value comparing OS between treatment groups was based on the 1-sided Cui-Hung-Wang weighted unstratified log-rank test.

Secondary: Sixty-Day Mortality Reported as Number of Participants Who Died Up to Day 60

End point title	Sixty-Day Mortality Reported as Number of Participants Who Died Up to Day 60

End point description:

60-day mortality was defined as number of participants who died within 60 days from the first dose of study drug. Safety Population included all enrolled participants who received at least 1 dose of azacitidine alone or pevonedistat + azacitidine.

End point type	Secondary

End point timeframe:

Up to Day 60

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	223		
Units: participants	15	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates of Six-Month Survival Rate

End point title	Kaplan-Meier Estimates of Six-Month Survival Rate

End point description:

Kaplan-Meier estimates for the probability (expressed as a percentage) of participants that survived at the end of Month 6 from randomization are presented. ITT Population included all participants who were randomized. Subjects analysed is 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	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	174		
Units: percentage probability				
number (confidence interval 95%)	0.825 (0.767 to 0.869)	0.810 (0.752 to 0.856)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates of One-Year Survival Rate

End point title	Kaplan-Meier Estimates of One-Year Survival Rate

End point description:

Kaplan-Meier estimates for the probability (expressed as a percentage) of participants that survived at the end of the first year from randomization are presented. ITT Population included all participants who were randomized. Subjects analysed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Year 1

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	137		
Units: percentage probability				
number (confidence interval 95%)	0.693 (0.626 to 0.751)	0.646 (0.578 to 0.706)		

Statistical analyses

No statistical analyses for this end point

Secondary: Thirty-Day Mortality Reported as Number of Participants Who Died Up to Day 30

End point title	Thirty-Day Mortality Reported as Number of Participants Who Died Up to Day 30

End point description:

30-day mortality was defined as number of participants who died within 30 days from the first dose of study drug. Safety Population included all enrolled participants who received at least 1 dose of azacitidine alone or pevonedistat + azacitidine.

End point type	Secondary

End point timeframe:

Up to Day 30

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	223		
Units: participants	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Acute Myelogenous Leukemia (AML) Transformation in Higher-Risk Myelodysplastic Syndromes (HR MDS), Higher-Risk Chronic Myelomonocytic Leukemias (HR CMML) and HR MDS/CMML Participants

End point title	Time to Acute Myelogenous Leukemia (AML) Transformation in Higher-Risk Myelodysplastic Syndromes (HR MDS), Higher-Risk Chronic Myelomonocytic Leukemias (HR CMML) and HR

	MDS/CMML Participants

End point description:

Time to AML transformation in HR MDS & CMML participants: time from randomization to documented AML transformation as determined by independent review committee(IRC) assessment. Participants who died before progression to AML were censored. Transformation to AML was defined, according to WHO classification, as a participant having 20% blasts in blood or marrow & increase of blast count by 50%.ITT Population=all randomized participants. Subjects analysed: number (no.) of participants with data available for analyses. 'n'=no. of participants with data available for analysis for given category. 999 indicates median, lower and/or upper limit (UL) of 95% confidence interval (CI) not estimable due to low no. of participants with event.

End point type	Secondary

End point timeframe:

From randomization until transformation to AML (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	177		
Units: months				
median (confidence interval 95%)				
HR MDS Participants (n=163,161)	35.6 (26.51 to 999)	999 (23.29 to 999)		
HR CMML Participants (n=11,16)	999 (999 to 999)	999 (999 to 999)		
HR MDS/CMML Participants (n=174,177)	35.6 (29.04 to 999)	999 (24.28 to 999)		

Statistical analyses

Statistical analysis title	Time to AML Transformation in HR MDS Participants
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.562 [6]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.63

Notes:

[5] - HR:unadjusted stratified Cox proportional HazardRegression with stratification(IPSS-R risk groups=very high,high,or intermediate for HRMDS/CMML),treatment as factor.HR<1:better prevention of AML transformation in combination arm than azacitidine arm.

[6] - P-value comparing time to AML Transformation between treatment groups was based on 1-sided stratified log-rank test stratified by IPSS-R risk groups of very high, high, or intermediate for HR MDS.

Statistical analysis title	Time to AMLTransformation:HR MDS/CMML Participants
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.558 [8]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.663
upper limit	1.61

Notes:

[7] - HR:unadjusted stratified Cox proportional HazardRegression with stratification(IPSS-R risk groups=very high,high,or intermediate for HRMDS/CMML),treatment as factor.HR<1:better prevention of AML transformation in combination arm than azacitidine arm.

[8] - P-value comparing time to AML Transformation between treatment groups was based on 1-sided stratified log-rank test stratified by IPSS-R risk groups of very high, high, or intermediate for HR CMML/MDS.

Statistical analysis title	Time to AML Transformation in HR CMML Participants
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.603 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.512
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.068
upper limit	33.773

Notes:

[9] - HR:unadjusted stratified Cox proportional HazardRegression with stratification(IPSS-R risk groups=very high,high,or intermediate for HRMDS/CMML),treatment as factor.HR<1:better prevention of AML transformation in combination arm than azacitidine arm.

[10] - P-value comparing time to AML Transformation between treatment groups was based on 1-sided stratified log-rank test stratified by IPSS-R risk groups of very high, high, or intermediate for HR CMML.

Secondary: Number of Participants With Complete Remission (CR) and CR+ Complete Remission With Incomplete Blood Count Recovery (CRi)

End point title	Number of Participants With Complete Remission (CR) and CR+ Complete Remission With Incomplete Blood Count Recovery (CRi)

End point description:

CR for HR MDS or CMML is defined as <=5% myeloblasts with normal maturation of all cell lines in the bone marrow, and greater than or equal to >=11 gram per deciliter (g/dL) hemoglobin (Hgb),

>=100*10^9/liter (/L) platelets (pl),>=1.0*10^9/L neutrophils and 0% blasts in peripheral blood. CR for low-blast AML: morphologic leukemia-free state, neutrophils of more than 1.0*10^9/L and pl of >=100*10^9/L, transfusion independence, and no residual evidence of extramedullary leukemia. CR with incomplete blood count recovery (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). 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 randomization until CR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: participants	71	63		

Statistical analyses

Statistical analysis title	Complete Remission (CR) and CR+ Complete Remission

Statistical analysis description:

Number of Participants With Complete Remission (CR) and CR+Complete Remission with Incomplete Blood Count Recovery (CRi)

Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.374 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.18
upper limit	4.83

Notes:

[11] - P-value was obtained from a stratified Cochran-Mantel-Haenszel chi-square test stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Secondary: Number of Participants With CR and Marrow CR

End point title	Number of Participants With CR and Marrow CR

End point description:

Disease responses for HR MDS or CMML are based on the International Working Group (IWG) Response Criteria for MDS. CR for HR MDS or CMML is defined as <=5% myeloblasts with normal maturation of all cell lines in the bone marrow, and >=11 g/dL Hgb, >=100*10^9/L platelets (pl), >=1.0*10^9/L neutrophils and 0% blasts in peripheral blood. Marrow CR: Bone marrow: <=5% myeloblasts and decrease by >=50% over pretreatment. 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 randomization until CR or marrow CR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: participants	91	87		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With CR, Partial Remission (PR) and Hematologic Improvement (HI)

End point title	Number of Participants With CR, Partial Remission (PR) and Hematologic Improvement (HI)

End point description:

Disease responses for HR MDS/CMML based on Modified IWG Response Criteria for MDS. CR: <=5% myeloblasts with normal maturation of all bone marrow cell lines, >=11 g/dL Hgb, >=100*10^9/L pl, >=1.0*10^9/L neutrophils,0% blasts in peripheral blood. Marrow CR: Bone marrow: <=5% myeloblasts and decrease by >=50% over pretreatment. PR: all CR criteria met except bone marrow blasts >=50% decrease over pretreatment but still >5%. HI: Hgb increase >=1.5 g/dL if <11 g/dL; pl increase >=30*10^9/L if baseline>20*10^9/L or increase from <20*10^9/L to >20*10^9/L and by at least 100%; neutrophil increase by 100% and absolute increase of >0.5*10^9/L if baseline <1.0*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.

End point type	Secondary

End point timeframe:

From randomization until, CR, PR or HI (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: participants	77	76		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With CR and Marrow CR and PR

End point title	Number of Participants With CR and Marrow CR and PR

End point description:

Disease responses for HR MDS/CMML based on Modified IWG Response Criteria for MDS. CR: <=5% myeloblasts with normal maturation of all bone marrow cell lines, >=11 g/dL Hgb, >=100*10^9/L pl, >=1.0*10^9/L neutrophils,0% blasts in peripheral blood. Marrow CR: Bone marrow: <=5% myeloblasts and decrease by >=50% over pretreatment. PR: all CR criteria met except bone marrow blasts >=50% decrease over pretreatment but still >5%. 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 randomization until CR or Marrow CR and PR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: participants	91	87		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With CR and Marrow CR, PR and Hematologic Improvement (HI)

End point title	Number of Participants With CR and Marrow CR, PR and Hematologic Improvement (HI)

End point description:

Disease responses for HR MDS/CMML based on Modified IWG Response Criteria for MDS. CR: <=5% myeloblasts with normal maturation of all bone marrow cell lines, >=11 g/dL Hgb, >=100*10^9/L pl, >=1.0*10^9/L neutrophils,0% blasts in peripheral blood. Marrow CR: Bone marrow: <=5% myeloblasts and decrease by >=50% over pretreatment. PR: all CR criteria met except bone marrow blasts >=50% decrease over pretreatment but still>5%. HI: Hgb increase >=1.5 g/dL if baseline <11 g/dL; pl increase >=30*10^9/L if baseline>20*10^9/L or increases from <20*10^9/L to >20*10^9/L and by at least 100%; neutrophil increases by 100% and absolute increases of >0.5*10^9/L if baseline <1.0*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.

End point type	Secondary

End point timeframe:

From randomization until CR, marrow CR, PR or HI (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: participants	112	117		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Overall Response (OR)

End point title	Number of Participants With Overall Response (OR)

End point description:

Disease responses for HR MDS/CMML based on Modified IWG Response Criteria for MDS; for low-blast AML on Revised IWG Response Criteria for AML. Overall response=CR or PR for HR MDS/CMML and CR+CRi+PR for low-blast AML. CR for HR MDS/CMML: <=5% myeloblasts with normal maturation of all bone marrow cell lines, >=11 g/dL Hgb, >=100*10^9/L pl, >=1.0*10^9/L neutrophils, 0% blasts in peripheral blood & PR:all CR criteria met except bone marrow blasts >=50% decrease over pretreatment but still>5%. For low-blast AML-CR:morphologic leukemia-free state>1.0*10^9 neutrophils, >=100*10^9/L pl, transfusion independence, no residual evidence of extramedullary leukemia; CR with incomplete blood count recovery (CRi):fulfill CR criteria except residual neutropenia <1.0*10^9/L or pl <100*10^9/L; PR:all CR hematological values but >=50% decrease in bone marrow aspirate. REP included all participants who received at least 1 dose of study drug & had a Baseline and at least 1 postbaseline disease assessment.

End point type	Secondary

End point timeframe:

From randomization until CR and PR or CR, CRi and PR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: participants	73	64		

Statistical analyses

Statistical analysis title	Number of Participants with OR
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-4.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.72
upper limit	4.39

Notes:

[12] - P-value was obtained from a stratified Cochran-Mantel-Haenszel chi-square test stratified by low-blast AML, Revised International Prognostic Scoring System (IPSS-R) risk groups of very high, high, or intermediate for HR MDS/CMML.

Secondary: Number of Participants With Overall Response 2 (OR2)

End point title	Number of Participants With Overall Response 2 (OR2)

End point description:

AML participants.CR:≤5% myeloblasts with normal maturation of all bone marrow(BM)cell lines,≥11g/dL Hgb,≥100*10^9/L pl,≥1.0*10^9/L neutrophils(NL),0% blasts in peripheral blood;PR:all CR criteria met except BM blasts ≥50% decrease over pretreatment but still >5%;HI:Hgb increase(inc) ≥1.5g/dL if baseline(BL)<11 g/dL;pl inc≥30*10^9/L if BL>20*10^9/L or inc from <20*10^9/L to >20*10^9/L & by 100%;NL inc by 100%;absolute inc of >0.5*10^9/L if BL<100*10^9/L.For low-blast AML-CR:morphologic leukemia-free state >1.0*10^9 NL,≥100*10^9/L pl,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 or pl<100*10^9/L;PR:all CR hematological values but ≥50% decrease in BM aspirate.No. of responders determined by independent review committee(IRC).REP.Data is reported for responders.3 participants not counted as responders for OR2 as IRC assessed these participants as non-responders.

End point type	Secondary

End point timeframe:

From randomization until, CR, PR or HI or CR, CRi or PR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: participants	94	94		

Statistical analyses

Statistical analysis title	Number of Participants with OR2
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.891 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.03
upper limit	9.15

Notes:

[13] - P-value was obtained from a stratified Cochran-Mantel-Haenszel chi-square test stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Secondary: Duration of Complete Remission + Complete Remission With Incomplete Blood Count Recovery (CRi)

End point title	Duration of Complete Remission + Complete Remission With Incomplete Blood Count Recovery (CRi)

End point description:

Duration of CR is 1st documented CR to 1st documentation of PD or relapse from CR (participants with low-blast AML). Disease responses for low-blast AML were based on Revised IWG Response Criteria for AML. CR:≤5% myeloblasts with normal maturation of all cell lines in bone marrow, & ≥11g/dL Hgb, ≥100*10^9/liter(/L) pl, ≥1.0*10^9/L neutrophils & 0% blasts in peripheral blood. CR for low-blast AML: morphologic leukemia-free state, neutrophils of more than 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 criteria for CR except for residual neutropenia (<1.0*10^9/L) or thrombocytopenia (pl<100*10^9/L). REP included all participants who received at least 1 dose of study drug & had a Baseline & at least 1 postbaseline disease assessment. Data is reported for participants with CR & CRi. 999: upper limit of 95% CI was not estimable due to low no. of participants with event.

End point type	Secondary

End point timeframe:

From CR until first documentation of PD or relapse from CR or relapse after CR or PR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: months				
median (confidence interval 95%)	8.5 (3.02 to 999)	15.0 (3.94 to 999)		

Statistical analyses

Statistical analysis title	Duration

Statistical analysis description:

Duration of Complete Remission + Complete Remission with Incomplete Blood Count Recovery (CRi)

Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.373 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.306
upper limit	2.339

Notes:

[14] - Hazard ratio was based on an unadjusted unstratified Cox proportional hazard regression model with treatment as a factor in the model.
[15] - P-value comparing duration of CR+CRi between treatment groups was based on 1-sided unstratified log-rank.

Secondary: Duration of Complete Remission (CR)

End point title	Duration of Complete Remission (CR)

End point description:

Duration of CR is 1st documented CR to 1st documentation of PD/relapse from CR(participants with low-blast AML)/relapse after CR/PR(participants with HR MDS/CMML).Disease responses for HR MDS/CMML are based on Modified IWG Response Criteria for MDS & 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/dLHgb,≥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 more than 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 criteria for CR except for residual neutropenia(<1.0*10^9/L) or thrombocytopenia(pl<100*10^9/L).REP.Data is reported for participants with complete remission.999:UL of 95% CI was not estimable due to low no. of participants with event.

End point type	Secondary

End point timeframe:

From CR until first documentation of PD or relapse from CR or relapse after CR or PR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	57		
Units: months				
median (confidence interval 95%)	13.1 (6.93 to 29.08)	17.2 (13.96 to 999)		

Statistical analyses

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

	Azacitidine 75 mg/m^2
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.072 [17]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.679
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.402
upper limit	1.146

Notes:

[16] - Hazard ratio was based on an unadjusted stratified Cox proportional hazard regression model with stratification factors (low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML) and treatment as a factor in the model.

[17] - P-value was based on 1-sided log-rank test stratified by low-blast AML,IPSS-R risk groups of very high,high,or intermediate for HR MDS/CMML.

Secondary: Duration of Overall Response (OR)

End point title	Duration of Overall Response (OR)

End point description:

Duration of OR:response to 1st documentation of PD or relapse from CR for low-blast AML or relapse after CR or PR for HR MDS/CMML.Disease responses for HR MDS/CMML based on Modified IWG Response Criteria for MDS;for low-blast AML on Revised IWG Response Criteria for AML.Overall response=CR+PR for HR MDS/CMML & CR+Cri+PR for low-blast AML.CR for HR MDS/CMML:≤5% myeloblasts with normal maturation of all BM cell lines,≥11 g/dL Hgb,≥100*10^9/L pl,≥1.0*10^9/L NL,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 NL,≥100*10^9/L pl,transfusion independence,no residual evidence of extramedullary leukemia;CR with CRi:fulfill CR criteria except residual neutropenia<1.0*10^9/L or pl<100*10^9/L;PR:all CR hematological values but≥50% decrease in % of blasts in BM aspirate.REP.Responders were analyzed.999:upper limit of 95% CI not estimable due to fewer subjects with event.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	64		
Units: months				
median (confidence interval 95%)	18.3 (8.31 to 999)	17.1 (12.68 to 999)		

Statistical analyses

Statistical analysis title	Duration of Overall Response (OR)
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.32 [19]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.889
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.542
upper limit	1.458

Notes:

[18] - Hazard ratio was based on an unadjusted stratified Cox proportional hazard regression model with stratification factors (low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML) and treatment as a factor in the model.

[19] - P-value comparing duration of PR or better response between treatment groups was based on 1-sided log-rank test stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Secondary: Duration of Overall Response 2 (OR2)

End point title	Duration of Overall Response 2 (OR2)

End point description:

Duration of OR2:1st documentation of CR+PR+HI to 1st documentation of PD/relapse after CR/PR for responders(CR+PR+HI=HR MDS/CMML;CR,CRi,PR=low-blast AML).For HR MDS/CMML-CR:≤5%myeloblasts+normal maturation of all BM cell lines,≥11g/dL Hgb,≥100*10^9/L pl,≥1.0*10^9/L NL,0%peripheral blood blasts;PR:CR criteria except BMblasts≥50%decrease(pretreatment),still>5%;HI:Hgb inc≥1.5g/dL if BL<11g/dL;pl inc≥30*10^9/L if BL>20*10^9/L or inc from<20*10^9/L to>20*10^9/L by ≥100%;NL100% inc &absolute >0.5*10^9/L inc if BL<1.0*10^9/L.For low-blast AML-CR:morphologic leukemia-free state,>1.0*10^9 NL,≥100*10^9/L pl,transfusion independence,no residual evidence of extramedullary leukemia;CRi:CR criteria except residual neutropenia<1.0*10^9/L or pl<100*10^9/L;PR:CR hematological values but≥50%decrease in BM aspirate.REP.As duration of OR2 could be derived based on criteria for HR MDS/CMML subjects,3 non-responders(per IRC)included in analysis.999:95%CI(UL)not estimable due to

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	96		
Units: months				
median (confidence interval 95%)	18.3 (11.17 to 30.92)	18.9 (15.01 to 999)		

Statistical analyses

Statistical analysis title	Duration of Overall Response 2 (OR2)
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.151 [21]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.796
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.514
upper limit	1.231

Notes:

[20] - Hazard ratio was based on an unadjusted stratified Cox proportional hazard regression model with stratification factors (low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML) and treatment as a factor in the model.
[21] - P-value comparing duration of overall response 2 between treatment groups was based on 1-sided log-rank test stratified by low blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

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. Subjects analyzed is the number of participants from a subset of the ITT Population who were transfusion dependent at Baseline. 'n' is the number of participants who were transfusion dependent at Baseline for the specified category.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	129		
Units: percentage of participants				
number (not applicable)				
RBCs-transfusion Independence (n=131,122)	44.3	47.5		
Platelet-transfusion Independence (n=45,33)	48.9	45.5		

Statistical analyses

Statistical analysis title	Platelet-transfusion Independence
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.477 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.84
upper limit	18.97

Notes:

[22] - P-value was obtained from a stratified Cochran-Mantel-Haenszel chi-square test.

Statistical analysis title	RBC-transfusion Independence
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.573 [23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	3.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.02
upper limit	15.55

Notes:

[23] - P-value was obtained from a stratified Cochran-Mantel-Haenszel chi-square test.

Secondary: Duration of Red Blood Cells (RBCs) and Duration of Platelet-transfusion Independence and Duration of Red Blood Cells (RBCs) and Platelet-transfusion Independence

End point title	Duration of Red Blood Cells (RBCs) and Duration of Platelet-transfusion Independence and Duration of Red Blood Cells (RBCs) and Platelet-transfusion Independence

End point description:

Duration of RBC and platelet transfusion independence was defined as the longest time between the last

RBC and/or platelet transfusion before the start of the RBC and/or platelet transfusion-independent period and the first RBC and/or platelet transfusion after the start of the transfusion-independent period, which occurs >= 8 weeks later. ITT Population included all participants who were randomized. 'n' is the number of participants who achieved transfusion independence for the specified category, with data available for analysis.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: months				
median (confidence interval 95%)				
RBC Transfusion Independence(n=58,58)	15.6 (10.18 to 28.09)	13.5 (9.07 to 16.66)		
Platelet Transfusion Independence (n=22,15)	14.9 (5.09 to 23.23)	11.6 (2.73 to 16.26)		
Transfusion Independence (n=63,59)	12.0 (8.90 to 19.48)	13.5 (10.38 to 16.66)		

Statistical analyses

Statistical analysis title	Duration of RBC Transfusion Independence
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.774 [25]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.231
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.715
upper limit	2.119

Notes:

[24] - HR:unadjusted Cox Proportional Hazard regression;stratification(low-blast AML,IPSS-R risk groups=very high,high,intermediate for HRMDS/CMML),treatment as factor.HR<1:longer duration of transfusion independence in combination arm than azacitidine arm.

[25] - P-value comparing duration of RBC or platelet transfusion between treatment groups was based on 1-sided log-rank test stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Statistical analysis title	Duration of Platelet Transfusion Independence
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2

Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.801 [27]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.533
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.567
upper limit	4.147

Notes:

[26] - HR:unadjusted Cox Proportional Hazard regression;stratification(low-blast AML,IPSS-R risk groups=very high,high,intermediate for HRMDS/CMML),treatment as factor.HR<1:longer duration of transfusion independence in combination arm than azacitidine arm.

[27] - P-value comparing duration of platelet transfusion between treatment groups was based on 1-sided log-rank test stratified by low blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Statistical analysis title	Duration of Transfusion Independence
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.45 [29]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.968
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.614

Notes:

[28] - HR:unadjusted Cox Proportional Hazard regression;stratification(low-blast AML,IPSS-R risk groups=very high,high,intermediate for HRMDS/CMML),treatment as factor.HR<1:longer duration of transfusion independence in combination arm than azacitidine arm.

[29] - P-value comparing duration of RBC or platelet transfusion between treatment groups was based on 1-sided log-rank test stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Secondary: Time to First Complete Remission (CR) or Partial Remission (PR) or Complete Remission With Incomplete Blood Count Recovery (CRi)

End point title	Time to First Complete Remission (CR) or Partial Remission (PR) or Complete Remission With Incomplete Blood Count Recovery (CRi)

End point description:

Time to 1st CR/PR:time from randomization to 1st documented CR/PR,whichever occurs first.Disease responses for HR MDS or CMML or low-blast AML cycle 6 are based on Modified IWG Response Criteria for MDS & for low-blast AML on Revised IWG Response Criteria for AML.For HR MDS or CMML-CR:≤5% myeloblasts with normal maturation of all BM cell lines,≥11 g/dL Hgb,≥100*10^9/L pl,≥1.0*10^9/L NL,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 NL, pl≥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 or pl <100*10^9/L;PR: all CR hematological values but with a decrease of ≥50% in % of blasts to 5% to

median, & upper limit of 95% CI was not estimable due to low no. of participants with event.

End point type	Secondary

End point timeframe:

From randomization until CR or PR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: months				
median (confidence interval 95%)	999 (12.12 to 999)	999 (24.61 to 999)		

Statistical analyses

Statistical analysis title	Time to 1st CR/PR/Cr With Incomplete Blood CRi
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.228 [31]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.628
upper limit	1.234

Notes:

[30] - Hazard ratio was based on an unadjusted stratified Cox proportional hazard regression model with stratification factors (low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML) and treatment as a factor in the model.

[31] - P-value comparing time to first CR or PR or CRi (low-blast AML) between treatment groups was based on 1-sided stratified log-rank test stratified by low-blast AML,IPSS-R risk groups of very high, high,or intermediate for HR MDS/CMML.

Secondary: Number of Participants With Hematologic Improvement (HI)

End point title	Number of Participants With Hematologic Improvement (HI)

End point description:

Disease responses for HR MDS/CMML based on Modified IWG Response Criteria for MDS. HI: Hgb increase >=1.5 g/dL if baseline <11 g/dL; pl increase >=30*10^9/L if baseline >20*10^9/L or increase from <20*10^9/L to >20*10^9/L by at least 100%; neutrophil increase by 100% and absolute increase of >0.5*10^9/L if baseline <1.0*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. Subjects analysed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

From randomization until HI (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	163		
Units: participants	76	70		

Statistical analyses

Statistical analysis title	Number of Participants With HI
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32 [32]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-5.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.36
upper limit	5.44

Notes:

[32] - P-value was obtained from a stratified Cochran-Mantel-Haenszel chi-square test.

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

End point title	Number 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%. ITT Population included all participants who were randomized.

End point type	Secondary

End point timeframe:

From randomization until transformation to AML or until initiation of subsequent therapy (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: participants	3	9		

Statistical analyses

Statistical analysis title	Inpatient Hospital Admissions
Statistical analysis description:	
Number of Participants With at Least 1 Inpatient Hospital Admissions Related to HR MDS, CMML or Low-blast AML	
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Rate Difference
Point estimate	2.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	5.58

Secondary: Time to Progressive Disease (PD), Relapse After CR (Low-blast AML), Relapse After CR or PR (HR MDS/CMML), or Death

End point title	Time to Progressive Disease (PD), Relapse After CR (Low-blast AML), Relapse After CR or PR (HR MDS/CMML), or Death

End point description:

Time to PD,relapse after CR(low-blast AML),relapse after CR/PR(HR MDS/CMML),or death,defined as time from date of randomization until date of 1st documentation of PD,relapse after CR(low-blast AML),relapse after CR/PR(HR MDS/CMML),or death due to any cause,whichever occurs first.In HR MDS/CMML,PD:Participants with<5% blasts:≥50% inc >5% blasts,with 5%-9% blasts:≥50% inc>10% blasts,with 10%-19% blasts:≥50% inc>20% blasts,with20%-30% blasts,at least 50% decrement from maximum remission/response in granulocytes or pl or reduction in Hgb by≥2 g/dL/new transfusion dependence.Relapse after CR or PR: return to pretreatment bone marrow blast %/Decrement of≥50% from maximum remission/response levels in granulocytes/pl/reduction in Hgb conc.≥1.5 g/dL/transfusion dependence.In AML,PD:>50% inc in bone marrow blasts to>30% blasts,>50% inc in circulating blasts to>30% blasts in peripheral blood,Development of extramedullary disease/new sites of extramedullary leukemia.ITT Population.

End point type	Secondary

End point timeframe:

From randomization until PD, relapse after CR, or relapse after CR or PR, or death due to any cause, whichever occurs first (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: months				
median (confidence interval 95%)	11.8 (10.25 to 13.31)	13.1 (11.01 to 15.84)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Time to Progressive Disease (PD), Relapse after CR (Low-blast AML), Relapse After CR or PR (HR MDS/CMML), or Death

Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.084 [34]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.858
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.689
upper limit	1.067

Notes:

[33] - Hazard ratio was based on a stratified Cox proportional hazard regression model stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML, with treatment as a factor in the model.

[34] - P-value was obtained from a stratified 1-sided log-rank test stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Secondary: Change From Baseline in Health-Related Quality of Life (HRQOL) Using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire- Core 30

End point title	Change From Baseline in Health-Related Quality of Life (HRQOL) Using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30

End point description:

The EORTC QLQ-C30 contains 30 items across 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties) and a global health status(GHS)/QOL scale. Most of the 30 items have 4 response levels (not at all, a little, quite a bit, and very much), with 2 questions relying on a 7-point numeric rating scale. Raw scores are converted into scale scores ranging from 0 to 100.For the functional scales and the global health status/QOL scale, higher scores represent better QOL; for the symptom scales, lower scores represent better QOL.The change from baseline at end of treatment is reported. ITT Population included all participants who were randomised. All participants with PRO measurements at baseline and with data available at end of treatment were analysed for this endpoint.

End point type	Secondary

End point timeframe:
Baseline, at approximately 58 months

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	210		
Units: score on a scale				
arithmetic mean (standard deviation)				
GHS/QoL Score: BL (n=211,210)	60.3 (± 22.11)	61.6 (± 21.13)		
GHS/QoL Score: Change from BL (n=146,124)	-3.0 (± 25.93)	-8.4 (± 26.89)		
Physical Functioning (PF) Score: BL(n=211,210)	69.4 (± 22.63)	75.7 (± 20.38)		
PF Score: Change from BL (n=146,125)	-7.5 (± 22.82)	-13.4 (± 27.51)		
Role Functioning (RF) Score: BL (n=211,210)	66.9 (± 30.88)	73.7 (± 28.55)		
RF Score: Change from BL(n=146,126)	-11.8 (± 35.41)	-18.3 (± 36.72)		
Emotional Functioning (EF) Score: BL (n=211,210)	76.0 (± 20.96)	77.6 (± 22.10)		
EF Score: Change from BL(n=146,124)	-2.5 (± 23.80)	-5.9 (± 22.41)		
Cognitive Functioning (CF) Score: BL (n=211,210)	84.6 (± 18.29)	86.1 (± 17.60)		
CF Score: Change from BL (n=146,125)	-7.2 (± 22.65)	-10.4 (± 24.38)		
Social Functioning (SF) Score: BL (n=211,208)	79.3 (± 25.37)	78.8 (± 25.82)		
SF Score: Change from BL (n=146,122)	-13.7 (± 33.89)	-16.5 (± 34.78)		
Fatigue Score: BL (n=211,210)	38.5 (± 25.44)	33.8 (± 24.24)		
Fatigue Score: Change from BL (n=146,126)	6.6 (± 26.41)	12.3 (± 31.22)		
Nausea/Vomiting Score: BL (n=211,210)	4.6 (± 11.39)	4.7 (± 10.96)		
Nausea/Vomiting Score:Change from BL(n=146,125)	2.4 (± 19.08)	1.9 (± 15.00)		
Pain Score: BL (n=211,210)	20.9 (± 25.55)	19.4 (± 26.42)		
Pain Score: Change from BL (n=146,125)	5.8 (± 30.36)	6.8 (± 33.34)		
Dyspnoea Score: BL (n=211,210)	25.4 (± 29.83)	24.4 (± 28.90)		
Dyspnoea Score:Change from BL(n=146,124)	5.9 (± 28.95)	5.9 (± 29.46)		
Insomnia Score: BL (n=211,210)	27.2 (± 27.96)	25.7 (± 30.68)		
Insomnia Score: Change from BL (n=145,124)	3.2 (± 34.32)	4.6 (± 34.09)		
Appetite Loss Score: BL (n=211,210)	23.4 (± 29.29)	15.6 (± 23.99)		
Appetite Loss Score: Change from BL (n=146,125)	4.6 (± 38.68)	16.0 (± 34.03)		
Constipation Score: BL (n=211,210)	14.7 (± 24.78)	13.8 (± 22.47)		
Constipation Score:Change from BL(n=146,125)	5.5 (± 29.56)	5.1 (± 28.42)		
Diarrhoea Score: BL (n=211,210)	7.6 (± 18.84)	7.0 (± 16.75)		

Diarrhoea Score: Change from BL (n=146,124)	3.0 (± 22.80)	1.9 (± 27.65)		
Financial Difficulties (FD) Score: BL (n=211,208)	14.2 (± 25.37)	18.4 (± 26.76)		
FD Score: Change from BL (n=146,122)	5.9 (± 27.03)	7.4 (± 30.46)		
QLQ-C30 Summary Score: BL (n=211,208)	77.9 (± 14.90)	80.5 (± 15.08)		
QLQ-C30 Summary Score:Change from BL (n=145,120)	-6.1 (± 18.84)	-8.6 (± 17.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival in Participants Who Have TP53 Mutations, 17p Deletions, and/or Are Determined to be in an Adverse Cytogenetic Risk Group

End point title	Event-Free Survival in Participants Who Have TP53 Mutations, 17p Deletions, and/or Are Determined to be in an Adverse Cytogenetic Risk Group

End point description:

Event was defined as death or transformation to AML in participants with MDS or CMML, whichever occurred first. Transformation to AML was 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%. Event was defined as death in participants with low-blast AML. ITT Population included all participants who were randomized.

End point type	Secondary

End point timeframe:

From randomization until transformation to AML if eligible or death (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: months				
median (confidence interval 95%)	12.8 (8.44 to 14.32)	14.6 (9.99 to 18.99)		

Statistical analyses

Statistical analysis title	Event-Free Surviva

Statistical analysis description:

Event-Free Survival in Participants who have TP53 Mutations, 17p Deletions, and/or are Determined to be in an Adverse Cytogenetic Risk Group

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

Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.24 [36]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.877
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.608
upper limit	1.263

Notes:

[35] - HR:unadjusted stratified Cox proportional hazard regression with stratification factors (IPSS-R risk groups=very high,high,or intermediate for HRMDS/CMML),treatment as factor.HR<1:better prevention of EFS in combination arm than azacitidine arm.

[36] - P-value comparing EFS between treatment groups was based on 1-sided log-rank test stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Secondary: Number of Participants With Overall Response in Participants Who Have TP53 Mutations, 17p Deletions, and/or Are Determined to be in an Adverse Cytogenetic Risk Group

End point title	Number of Participants With Overall Response in Participants Who Have TP53 Mutations, 17p Deletions, and/or Are Determined to be in an Adverse Cytogenetic Risk Group

End point description:

Disease responses for HR MDS/CMML based on Modified IWG Response Criteria for MDS;for low-blast AML on Revised IWG Response Criteria for AML.Overall response=CR+PR for HR MDS/CMML & CR+CRi+PR for low-blast AML.CR for HR MDS/CMML:≤5% myeloblasts with normal maturation of all BM cell lines,≥11 g/dL Hgb,≥100*10^9/L pl,≥1.0*10^9/L NL,0% blasts in peripheral blood and 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 NL,≥100*10^9/L pl,transfusion independence,no residual evidence of extramedullary leukemia;CR with incomplete blood count recovery(CRi):fulfill CR criteria except residual neutropenia<1.0*10^9/L or pl<100*10^9/L;PR:all CR hematological values but≥50% decrease in the percentage of blasts to 5% to 25% in bone marrow aspirate.ITT Population.Subjects analysed:participants with data available for analyses.'n':participants with data available for analysis for specified category.

End point type	Secondary

End point timeframe:

From randomization until CR, CRi and PR (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
OR: HR MDS/CMML Participants (n=52,54)	14	13		
OR: Low-blast AML Participants (n=37,32)	13	12		

Statistical analyses

Statistical analysis title	ORR: Low-blast AML Participants
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84 [37]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	2.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.39
upper limit	25.12

Notes:

[37] - P-value for Low-blast AML was obtained from an unstratified Cochran-Mantel-Haenszel chi-square test.

Statistical analysis title	OR: HR MDS/CMML Participants
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.683 [38]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-2.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.44
upper limit	13.75

Notes:

[38] - P-value for HR MDS/CMML was obtained from a stratified Cochran-Mantel-Haenszel chi-square test

Secondary: Number of Participants With Overall Response by Cycle 6

End point title	Number of Participants With Overall Response by Cycle 6

End point description:

Responses for HR MDS/CMML are based on Modified International Working Group (IWG) Response Criteria for MDS and for low-blast AML on Revised IWG Response Criteria for AML.Overall response=CR & PR for HR MDS/CMML & CR+CR with CRi+PR for low-blast AML.CR for HR MDS/CMML:≤5% myeloblasts with normal maturation of all bone marrow cell lines,≥11g/dL Hgb,≥100*10^9/L pl,≥1.0*10^9/L neutrophils, 0% blasts in peripheral blood, and PR:all CR criteria met except bone marrow blasts≥50% decrease over pretreatment but still >5%.For low-blast AML-CR:morphologic leukemia-free state,>1.0*10^9 neutrophils,≥100*10^9/L pl, transfusion independence,no residual evidence of extramedullary leukemia;CRi:fulfill CR criteria except residual neutropenia <1.0*10^9/L/thrombocytopenia (pl<100*10^9/L); PR:all CR hematological values but≥50% decrease in percentage of blasts to 5%-25% in bone marrow aspirate.REP used.'n' is the no. of participants with data available for analysis for the specified category.

End point type	Secondary

End point timeframe:

Up to Cycle 6 (up to approximately Day 168)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	208		
Units: participants				
Overall Response for HR MDS/CMML (n=157,163)	36	29		
Overall Response for Low-blast AML (n=49,45)	13	22		

Statistical analyses

Statistical analysis title	Overall Response for HR MDS/CMML
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261 [39]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	-5.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.95
upper limit	3.68

Notes:

[39] - P-value was obtained from a stratified Cochran-Mantel-Haenszel chi-square test stratified by IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Statistical analysis title	Overall Response for Low-blast AML
Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [40]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute Rate Difference
Point estimate	22.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.22
upper limit	41.49

Notes:

[40] - P-value was obtained from an unstratified Cochran-Mantel-Haenszel chi-square test.

Secondary: Overall Survival in Participants Who Have TP53 Mutations, 17p Deletions, and/or Are Determined to be in an Adverse Cytogenetic Risk Group

End point title	Overall Survival in Participants Who Have TP53 Mutations, 17p Deletions, and/or Are Determined to be in an Adverse Cytogenetic Risk Group

End point description:

OS was calculated from date of randomization to the date of death due to any cause. Participants without documented death at the time of the analysis were censored as of the date the participant was last known to be alive. ITT Population included all participants who were randomized.

End point type	Secondary

End point timeframe:

From randomization until death (up to approximately 42 months)

End point values	Azacitidine 75 mg/m^2	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: months				
median (confidence interval 95%)	12.8 (10.84 to 14.78)	16.1 (11.40 to 20.24)		

Statistical analyses

Statistical analysis title	Overall Survival in Participants

Statistical analysis description:

Overall Survival in Participants who have TP53 Mutations, 17p Deletions, and/or are Determined to be in an Adverse Cytogenetic Risk Group

Comparison groups	Azacitidine 75 mg/m^2 v Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.145 [42]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.826

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.178

Notes:

[41] - HR:unadjusted stratified Cox proportional hazard regression with stratification factors(IPSS-R risk groups of very high,high,intermediate) and treatment as factor in model.HR<1: longer survival time in combination arm than azacitidine arm.

[42] - P-value comparing OS between treatment groups was based on 1-sided log-rank test stratified by low-blast AML, IPSS-R risk groups of very high, high, or intermediate for HR MDS/CMML.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to end of study (up to approximately 6.9 years)

Adverse event reporting additional description:

The Safety Population included all participants who received at least 1 dose of study drug (i.e., pevonedistat + azacitidine or single-agent azacitidine).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

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

Reporting group description:

Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9 and pevonedistat 20 mg/m^2 IV infusion, on Days 1, 3, and 5 in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

Reporting group title	Azacitidine 75 mg/m^2

Reporting group description:

Participants were administered azacitidine 75 mg/m^2 IV or SC injection on Days 1 to 5, Days 8 and 9, in 28-day treatment cycles until disease progression or unacceptable toxicity or up to a maximum of 63 cycles.

Serious adverse events	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2	
Total subjects affected by serious adverse events			
subjects affected / exposed	156 / 223 (69.96%)	145 / 220 (65.91%)	
number of deaths (all causes)	150	153	
number of deaths resulting from adverse events	42	36	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	3 / 223 (1.35%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 223 (0.00%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (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			
Non-cardiac chest pain			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (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	6 / 223 (2.69%)	16 / 220 (7.27%)	
occurrences causally related to treatment / all	0 / 6	5 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Visceral pain			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	1 / 223 (0.45%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Fatigue			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 223 (0.90%)	3 / 220 (1.36%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 223 (0.45%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site inflammation			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 223 (0.45%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Organising pneumonia			
subjects affected / exposed	0 / 223 (0.00%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 223 (0.00%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bronchiectasis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 223 (0.45%)	3 / 220 (1.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal stenosis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 223 (0.45%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 223 (1.35%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 223 (0.90%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			

subjects affected / exposed	2 / 223 (0.90%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 223 (0.45%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Product contamination microbial			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Occult blood			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 223 (0.90%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system injury			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 223 (0.00%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hand fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyphaema			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractoriness to platelet transfusion			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Procedural haemorrhage			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thermal burn			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemorrhage			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silent myocardial infarction			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 223 (0.45%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			

subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	6 / 223 (2.69%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 6	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 223 (0.90%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 223 (1.35%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Atrioventricular block complete			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (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 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 223 (0.45%)	3 / 220 (1.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia with Lewy bodies			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			

subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 223 (0.00%)	3 / 220 (1.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	3 / 223 (1.35%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
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	13 / 223 (5.83%)	10 / 220 (4.55%)	
occurrences causally related to treatment / all	10 / 17	18 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			

subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukostasis syndrome			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukocytosis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	43 / 223 (19.28%)	35 / 220 (15.91%)	
occurrences causally related to treatment / all	37 / 74	30 / 52	
deaths causally related to treatment / all	0 / 0	1 / 1	
Splenic infarction			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	10 / 223 (4.48%)	4 / 220 (1.82%)	
occurrences causally related to treatment / all	15 / 15	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenic purpura			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	6 / 223 (2.69%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	5 / 8	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pure white cell aplasia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctival haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gingival bleeding			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 223 (0.90%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	4 / 223 (1.79%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 223 (0.00%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal ulcer haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematuria			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Polypoid cystitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spondylitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall haematoma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 223 (1.35%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	0 / 223 (0.00%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Arthralgia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (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			
Abdominal infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 223 (0.90%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 223 (0.45%)	5 / 220 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 3	
Cellulitis			
subjects affected / exposed	9 / 223 (4.04%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	1 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 223 (0.45%)	3 / 220 (1.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 223 (0.45%)	5 / 220 (2.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Herpes zoster			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	5 / 223 (2.24%)	6 / 220 (2.73%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lower respiratory tract infection fungal			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucormycosis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	33 / 223 (14.80%)	25 / 220 (11.36%)	
occurrences causally related to treatment / all	10 / 37	8 / 29	
deaths causally related to treatment / all	1 / 4	0 / 1	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perichondritis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			

subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 223 (0.90%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal abscess			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (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	3 / 223 (1.35%)	4 / 220 (1.82%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 223 (2.69%)	10 / 220 (4.55%)	
occurrences causally related to treatment / all	5 / 9	0 / 13	
deaths causally related to treatment / all	0 / 2	0 / 3	
Septic shock			
subjects affected / exposed	11 / 223 (4.93%)	6 / 220 (2.73%)	
occurrences causally related to treatment / all	4 / 13	1 / 8	
deaths causally related to treatment / all	3 / 8	0 / 4	
Serratia bacteraemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis septic			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
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 / 223 (0.90%)	5 / 220 (2.27%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 223 (3.14%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 223 (0.45%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperferritinaemia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 223 (0.00%)	2 / 220 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 223 (0.90%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			

subjects affected / exposed	0 / 223 (0.00%)	1 / 220 (0.45%)	
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	Pevonedistat 20 mg/m^2 + Azacitidine 75 mg/m^2	Azacitidine 75 mg/m^2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	210 / 223 (94.17%)	207 / 220 (94.09%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	13 / 223 (5.83%)	12 / 220 (5.45%)	
occurrences (all)	14	13	
Hypertension			
subjects affected / exposed	20 / 223 (8.97%)	14 / 220 (6.36%)	
occurrences (all)	20	21	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	34 / 223 (15.25%)	42 / 220 (19.09%)	
occurrences (all)	66	61	
Pyrexia			
subjects affected / exposed	53 / 223 (23.77%)	56 / 220 (25.45%)	
occurrences (all)	80	79	
Oedema peripheral			
subjects affected / exposed	29 / 223 (13.00%)	30 / 220 (13.64%)	
occurrences (all)	41	58	
Injection site pain			
subjects affected / exposed	12 / 223 (5.38%)	9 / 220 (4.09%)	
occurrences (all)	21	10	
Injection site erythema			
subjects affected / exposed	15 / 223 (6.73%)	20 / 220 (9.09%)	
occurrences (all)	47	53	
Fatigue			

subjects affected / exposed	42 / 223 (18.83%)	33 / 220 (15.00%)	
occurrences (all)	63	39	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	12 / 223 (5.38%)	14 / 220 (6.36%)	
occurrences (all)	18	14	
Epistaxis			
subjects affected / exposed	22 / 223 (9.87%)	22 / 220 (10.00%)	
occurrences (all)	29	36	
Dyspnoea			
subjects affected / exposed	26 / 223 (11.66%)	23 / 220 (10.45%)	
occurrences (all)	30	26	
Cough			
subjects affected / exposed	39 / 223 (17.49%)	25 / 220 (11.36%)	
occurrences (all)	47	30	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	21 / 223 (9.42%)	22 / 220 (10.00%)	
occurrences (all)	26	24	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 223 (8.52%)	11 / 220 (5.00%)	
occurrences (all)	52	13	
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 223 (7.62%)	11 / 220 (5.00%)	
occurrences (all)	42	13	
White blood cell count decreased			
subjects affected / exposed	16 / 223 (7.17%)	11 / 220 (5.00%)	
occurrences (all)	28	49	
Platelet count decreased			
subjects affected / exposed	33 / 223 (14.80%)	22 / 220 (10.00%)	
occurrences (all)	115	48	
Neutrophil count decreased			
subjects affected / exposed	33 / 223 (14.80%)	19 / 220 (8.64%)	
occurrences (all)	93	67	
Blood creatinine increased			

subjects affected / exposed	22 / 223 (9.87%)	14 / 220 (6.36%)	
occurrences (all)	36	15	
Blood bilirubin increased			
subjects affected / exposed	14 / 223 (6.28%)	6 / 220 (2.73%)	
occurrences (all)	24	10	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 223 (5.83%)	12 / 220 (5.45%)	
occurrences (all)	16	15	
Contusion			
subjects affected / exposed	20 / 223 (8.97%)	10 / 220 (4.55%)	
occurrences (all)	25	12	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 223 (11.66%)	20 / 220 (9.09%)	
occurrences (all)	38	22	
Dizziness			
subjects affected / exposed	19 / 223 (8.52%)	25 / 220 (11.36%)	
occurrences (all)	22	30	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	73 / 223 (32.74%)	77 / 220 (35.00%)	
occurrences (all)	182	191	
Leukopenia			
subjects affected / exposed	10 / 223 (4.48%)	14 / 220 (6.36%)	
occurrences (all)	30	23	
Febrile neutropenia			
subjects affected / exposed	15 / 223 (6.73%)	17 / 220 (7.73%)	
occurrences (all)	25	20	
Anaemia			
subjects affected / exposed	78 / 223 (34.98%)	82 / 220 (37.27%)	
occurrences (all)	154	214	
Thrombocytopenia			
subjects affected / exposed	71 / 223 (31.84%)	74 / 220 (33.64%)	
occurrences (all)	138	146	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	78 / 223 (34.98%)	63 / 220 (28.64%)	
occurrences (all)	111	89	
Haemorrhoids			
subjects affected / exposed	18 / 223 (8.07%)	6 / 220 (2.73%)	
occurrences (all)	20	7	
Diarrhoea			
subjects affected / exposed	61 / 223 (27.35%)	51 / 220 (23.18%)	
occurrences (all)	87	88	
Constipation			
subjects affected / exposed	82 / 223 (36.77%)	90 / 220 (40.91%)	
occurrences (all)	126	134	
Abdominal pain upper			
subjects affected / exposed	13 / 223 (5.83%)	12 / 220 (5.45%)	
occurrences (all)	13	14	
Abdominal pain			
subjects affected / exposed	22 / 223 (9.87%)	15 / 220 (6.82%)	
occurrences (all)	24	16	
Stomatitis			
subjects affected / exposed	16 / 223 (7.17%)	7 / 220 (3.18%)	
occurrences (all)	30	9	
Vomiting			
subjects affected / exposed	51 / 223 (22.87%)	46 / 220 (20.91%)	
occurrences (all)	71	68	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	15 / 223 (6.73%)	14 / 220 (6.36%)	
occurrences (all)	45	14	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 223 (15.70%)	30 / 220 (13.64%)	
occurrences (all)	43	36	
Back pain			
subjects affected / exposed	25 / 223 (11.21%)	18 / 220 (8.18%)	
occurrences (all)	34	25	
Myalgia			

subjects affected / exposed	14 / 223 (6.28%)	10 / 220 (4.55%)	
occurrences (all)	26	12	
Pain in extremity			
subjects affected / exposed	18 / 223 (8.07%)	22 / 220 (10.00%)	
occurrences (all)	21	25	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	22 / 223 (9.87%)	15 / 220 (6.82%)	
occurrences (all)	37	20	
Upper respiratory tract infection			
subjects affected / exposed	20 / 223 (8.97%)	21 / 220 (9.55%)	
occurrences (all)	24	25	
Pneumonia			
subjects affected / exposed	11 / 223 (4.93%)	19 / 220 (8.64%)	
occurrences (all)	12	20	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	29 / 223 (13.00%)	19 / 220 (8.64%)	
occurrences (all)	52	24	
Hyperuricaemia			
subjects affected / exposed	11 / 223 (4.93%)	15 / 220 (6.82%)	
occurrences (all)	12	18	
Decreased appetite			
subjects affected / exposed	38 / 223 (17.04%)	24 / 220 (10.91%)	
occurrences (all)	43	26	
Abnormal loss of weight			
subjects affected / exposed	7 / 223 (3.14%)	12 / 220 (5.45%)	
occurrences (all)	10	14	
Hypomagnesaemia			
subjects affected / exposed	16 / 223 (7.17%)	12 / 220 (5.45%)	
occurrences (all)	24	15	
Hypophosphataemia			
subjects affected / exposed	17 / 223 (7.62%)	7 / 220 (3.18%)	
occurrences (all)	54	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2018	The following changes were made as per Amendment 5: 1. Changed ORR by Cycle 6 from a primary endpoint of the study to a secondary endpoint of the study. 2. Provided a brief summary of the benefit-risk ratio of the combination of pevonedistat and azacitidine. 3. Removed an inconsistency between exclusion criterion 1 and exclusion criterion 7 and require that patients who are participating in any interventional study 14 days before the first dose of study drug be excluded from participation in the study. 4. Removed the sentence about completing a protocol deviation form. 5. Changed SAE reporting from a paper-based system to electronic data capture. 6. Added all response rates to the disclosures information for all primary and secondary endpoints.
31 March 2020	The following changes were made as per Amendment 7: 1. Updated sample and event size estimations for EFS and OS events in the ITT population, and updated estimates of length of time for patient accrual and follow-up. 2. Removed the calculation of quality-adjusted life-years (QALYs) from the planned analyses for patient-reported outcomes (PROs). 3. Added nonserious treatment-emergent adverse events (TEAEs) (≥5% in any arm) to the categories planned for safety analyses/tabulations. 4. Updated vial volume and dilution instructions for pevonedistat to include a vial volume of 4.4 milliliters (mL) and a diluent of 0.9% saline solution.
29 September 2020	The following changes were made as per Amendment 10: 1. Specified that alternative monitoring approaches such as remote source data verification may be used in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic. 2. Specified that nonessential protocol visits that do not require on-site sample collection and assessment may be completed via telemedicine.
26 March 2021	The following changes were made as per Amendment 12: 1. Updated and clarified text on the posttrial access (PTA) program and its duration. 2. Changed the alpha spending approach by using a 1-sided alpha of 0.0001 to test OS at second interim analysis (IA2) and the remaining 1-sided alpha of 0.0249 at the OS final analysis (FA), instead of using the O'Brien Fleming (OBF) method. 3. Removed EFS analyses in the HR MDS/CMML subpopulation from the multiple hierarchical testing procedures for IA2 and FA.
26 May 2021	The following changes were made as per Amendment 13: 1. Added clarification to outline the statistical analysis if the prespecified number of approximately 202 OS events for FA are expected (based on blinded study data) to be available close to the IA2, the IA2 (i.e., EFS FA) and the FA (i.e., OS FA) will be performed as a single analysis, when approximately 202 OS events and the adaptive EFS event size have occurred in patients with HR MDS. As originally planned, separate multiple hierarchical testing procedures for the United States (US) submission and the ex-US submission will be used to test the primary endpoint of EFS and the key secondary endpoint of OS in the HR MDS population (US submission), the ITT population (ex-US submission), and other disease populations at this single analysis, with a total 1-sided alpha of 0.025 for each procedure.
21 September 2021	The following changes were made as per Amendment 14: 1. Updated the name of the legal entity to Takeda Development Center Americas, Inc., 95 Hayden Avenue, Lexington, MA 02421.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported