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

## Summary

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

**Results information**

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

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | Pevonedistat-2001 |

**Additional study identifiers**

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

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

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

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

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

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

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

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

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

Arm description:

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

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

Dosage and administration details:

Azacitidine intravenous or subcutaneous formulation.

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

Arm description:

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

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

Dosage and administration details:

Pevonedistat intravenous or subcutaneous formulation.

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

Dosage and administration details:
Azacitidine intravenous or subcutaneous formulation.

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

## Baseline characteristics

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

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

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

## End points

### End points reporting groups

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

### Primary: Overall Survival (OS)

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

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

### Statistical analyses

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

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

Notes:

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

## Secondary: Event-Free Survival (EFS)

| | |
|---|---|
| End point title | Event-Free Survival (EFS) |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

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

Notes:

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

## Secondary: Six-month Survival Rate

| | |
|---|---|
| End point title | Six-month Survival Rate |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Month 6

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: One-year Survival Rate

| | |
|---|---|
| End point title | One-year Survival Rate |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Month 12

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Complete Remission (CR)

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + Pevonedistat 20 mg/m^2 |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.312 [3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Absolute Rate Difference |
| Point estimate | 9.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.83 |
| upper limit | 28.04 |

Notes:

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

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Azacitidine 75 mg/m^2 v Azacitidine 75 mg/m^2 + |

| | Pevonedistat 20 mg/m^2 |
|---|---|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.267 [4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.562 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 1.579 |

Notes:

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

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

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

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

Notes:

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

## Secondary: Percentage of Participants With Overall Response

| | |
|---|---|
| End point title | Percentage of Participants With Overall Response |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

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

| | |
|---|---|
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.301 [8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Absolute Rate Difference |
| Point estimate | 10.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.13 |
| upper limit | 30.18 |

Notes:

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

## Secondary: Percentage of Participants With CR by Cycle 4

| | |
|---|---|
| End point title | Percentage of Participants With CR by Cycle 4 |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

| | |
|---|---|
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.152 [9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Absolute Rate Difference |
| Point estimate | 13.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.49 |
| upper limit | 30.81 |

Notes:

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

## Secondary: Percentage of Participants With Overall Response by Cycle 4

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

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

| | |
|---|---|
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.436 [12] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.719 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.313 |
| upper limit | 1.653 |

Notes:

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

## Secondary: Duration of Complete Remission (CR)

| | |
|---|---|
| End point title | Duration of Complete Remission (CR) |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

| | |
|---|---|
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.62 [13] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.789 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.308 |
| upper limit | 2.02 |

Notes:

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

## Secondary: Duration of Overall Response

| | |
|---|---|
| End point title | Duration of Overall Response |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

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

Notes:

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

## Secondary: Time to First CR or PR

| | |
|---|---|
| End point title | Time to First CR or PR |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

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

Notes:

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

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

## Secondary: Time to Subsequent Therapy

| | |
|---|---|
| End point title | Time to Subsequent Therapy |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From date of randomization up to approximately 5 years

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

### Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|

Statistical analysis description:

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

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

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

Notes:

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

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

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

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 2 |

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

Notes:

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

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

Notes:

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

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

Notes:

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

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of participants with change from Baseline in ECOG performance status was measured on 6 point scale to assess participant’s performance status, where: Grade 0(Normal activity. Fully active, able to carry on all pre-disease activities without restriction); Grade 1(Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out light or sedentary work); Grade 2(In

bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours); Grade 3(In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50 percent of waking hours); Grade 4(100% bedridden. Completely disabled, cannot carry on any self-care, totally confined to bed or chair); Grade 5(Dead). ITT population=all participants who were randomized in the Safety Population. Only categories for which there was at least 1 participant are reported.

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

### Reporting groups

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

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Azacitidine 75 mg/m^2 |

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported