# Clinical trial results:
# A Phase 2/3 Study to Evaluate the Efficacy and Safety of Unesbulin in Unresectable or Metastatic, Relapsed or Refractory Leiomyosarcoma

## Summary

| | |
|---|---|
| EudraCT number | 2022-000073-12 |
| Trial protocol | HU ES DE IT PL NL FR |
| Global end of trial date | 17 July 2024 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 20 June 2025 |
| First version publication date | 20 June 2025 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | PTC596-ONC-008-LMS |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05269355 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | PTC Therapeutics, Inc. |
| Sponsor organisation address | 500 Warren Corp Centre Dr, Warren, United States, NJ 07059 |
| Public contact | Medical Information, PTC Therapeutics, Inc., +011 44 1-866-562-4620, medinfo@ptcbio.com |
| Scientific contact | Medical Information, PTC Therapeutics International Limited, +353 19068700, medinfo@ptcbio.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 | 17 July 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 17 July 2024 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess progression-free survival (PFS) of unesbulin plus dacarbazine versus placebo plus dacarbazine.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation (ICH) Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 May 2022 |
| 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 | United States: 202 |
| Country: Number of subjects enrolled | Australia: 9 |
| Country: Number of subjects enrolled | Brazil: 26 |
| Country: Number of subjects enrolled | Canada: 33 |
| Country: Number of subjects enrolled | France: 26 |
| Country: Number of subjects enrolled | Hungary: 11 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Poland: 1 |
| Country: Number of subjects enrolled | Spain: 18 |
| Country: Number of subjects enrolled | United Kingdom: 27 |
| Country: Number of subjects enrolled | Germany: 2 |
| Worldwide total number of subjects | 358 |
| EEA total number of subjects | 61 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| wk | |
|---|---|
| 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) | 256 |
| From 65 to 84 years | 101 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants were randomized 2:1 to 1 of the following treatment groups: 1. Unesbulin and Dacarbazine (N=239) or 2. Placebo and Dacarbazine (N=120). A total of 359 participants were randomized, of which 358 participants were treated.

### 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, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Unesbulin and Dacarbazine |

Arm description:

Participants received unesbulin 300 milligrams (mg) tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/square meter (m^2) intravenously (IV) once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Unesbulin |
| Investigational medicinal product code | PTC596 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Unesbulin was administered per schedule specified in the arm description.

| | |
|---|---|
| Investigational medicinal product name | Dacarbazine |
| Investigational medicinal product code | DTIC |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dacarbazine was administered per schedule specified in the arm description.

| | |
|---|---|
| **Arm title** | Placebo and Dacarbazine |

Arm description:

Participants received placebo matching to unesbulin tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m^2 IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PTC596 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

| | |
|---|---|
| Dosage and administration details:<br>Placebo matched to unesbulin was administered per schedule specified in the arm description. | |
| Investigational medicinal product name | Dacarbazine |
| Investigational medicinal product code | DTIC |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>Dacarbazine was administered per schedule specified in the arm description. | |

| **Number of subjects in period 1** | Unesbulin and Dacarbazine | Placebo and Dacarbazine |
|---|---|---|
| Started | 238 | 120 |
| Received at Least 1 Dose of Study Drug | 238 | 120 |
| Completed | 0 | 0 |
| Not completed | 238 | 120 |
| Adverse event, serious fatal | 3 | 5 |
| Consent withdrawn by subject | 18 | 5 |
| Physician decision | 6 | 4 |
| Other Than Specified | 5 | 1 |
| Adverse event, non-fatal | 15 | 8 |
| Progressive Disease | 104 | 68 |
| Study Terminated by Sponsor | 87 | 29 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Unesbulin and Dacarbazine |
| Reporting group description: | |
| Participants received unesbulin 300 milligrams (mg) tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/square meter (m^2) intravenously (IV) once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason. | |
| Reporting group title | Placebo and Dacarbazine |
| Reporting group description: | |
| Participants received placebo matching to unesbulin tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m^2 IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason. | |

| Reporting group values | Unesbulin and Dacarbazine | Placebo and Dacarbazine | Total |
|---|---|---|---|
| Number of subjects | 238 | 120 | 358 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 57.4 | 58.6 | |
| standard deviation | ± 10.98 | ± 11.04 | - |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 187 | 93 | 280 |
| Male | 51 | 27 | 78 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 36 | 26 | 62 |
| Not Hispanic or Latino | 170 | 87 | 257 |
| Unknown or Not Reported | 32 | 7 | 39 |
| Race<br>Units: Subjects | | | |
| Asian | 17 | 8 | 25 |
| American Indian/Alaska Native | 0 | 1 | 1 |
| Black/African American | 20 | 6 | 26 |
| Native Hawaiian/Other Pacific Islander | 1 | 0 | 1 |
| White/Caucasian | 157 | 92 | 249 |
| Other | 38 | 12 | 50 |
| Missing | 2 | 1 | 3 |
| Multiple | 3 | 0 | 3 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Unesbulin and Dacarbazine |

Reporting group description:

Participants received unesbulin 300 milligrams (mg) tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/square meter (m^2) intravenously (IV) once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

| | |
|---|---|
| Reporting group title | Placebo and Dacarbazine |

Reporting group description:

Participants received placebo matching to unesbulin tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m^2 IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

### Primary: Progression Free Survival (PFS) Per Independent Central Review Using Response Evaluation Criteria in Solid Tumors (RECIST) V1.1

| | |
|---|---|
| End point title | Progression Free Survival (PFS) Per Independent Central Review Using Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 |

End point description:

PFS was defined as the time from randomization to the documented disease progression or death due to any cause, whichever occurred first. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters (mm). The appearance of one or more new lesions was also considered progression. The modified intent-to-treat (mITT) set included randomized participants with 1 to 3 prior lines of therapy.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Up to approximately 2 years

| End point values | Unesbulin and Dacarbazine | Placebo and Dacarbazine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 105 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.6 (2.8 to 5.5) | 2.6 (1.5 to 3.0) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Unesbulin and Dacarbazine v Placebo and Dacarbazine |

| | |
|---|---|
| Number of subjects included in analysis | 314 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0017 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.45 |
| upper limit | 0.83 |

## Secondary: Objective Response Rate (ORR) Per Independent Central Review Using RECIST V1.1

| | |
|---|---|
| End point title | Objective Response Rate (ORR) Per Independent Central Review Using RECIST V1.1 |

End point description:

ORR was defined as percentage of participants who achieved a confirmed best overall response (BOR) of complete response (CR) or partial response (PR). CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The mITT set included randomized participants with 1 to 3 prior lines of therapy.

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

End point timeframe:

Up to approximately 2 years

| End point values | Unesbulin and Dacarbazine | Placebo and Dacarbazine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 105 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 8.1 (4.7 to 12.8) | 2.1 (0.3 to 7.3) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Disease Control Rate (DCR) Per Independent Central Review Using RECIST V1.1

| | |
|---|---|
| End point title | Disease Control Rate (DCR) Per Independent Central Review Using RECIST V1.1 |

End point description:

DCR was defined as percentage of participants who achieved a confirmed BOR of CR, PR, or at least 3 months of stable disease (SD). CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30%

decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. The mITT set included randomized participants with 1 to 3 prior lines of therapy.

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

End point timeframe:

Up to approximately 2 years

| **End point values** | Unesbulin and Dacarbazine | Placebo and Dacarbazine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 105 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 36.4 (29.7 to 43.5) | 27.1 (18.5 to 37.1) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

| End point title | Overall Survival |
|---|---|

End point description:

Overall survival was defined as the time in months from the randomization date to the date of death from any cause or date last known alive for those who did not die. The mITT set included randomized participants with 1 to 3 prior lines of therapy. '9999' represents 'due to limited number of participants with an event, median and upper limit of 95% confidence interval (CI) could not be calculated.'

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

End point timeframe:

Up to approximately 2 years

| **End point values** | Unesbulin and Dacarbazine | Placebo and Dacarbazine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 105 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9999 (10.4 to 9999) | 9999 (11.0 to 9999) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response Per Independent Central Review Using RECIST V1.

**1**

| End point title | Duration of Response Per Independent Central Review Using RECIST V1.1 |
|---|---|

End point description:

Duration of response was defined as the time from the date of first confirmed response of CR or PR to the date of the first documented disease progression or death due to any cause, whichever occurred first. CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Disease progression: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. The mITT set included randomized participants with 1 to 3 prior lines of therapy. '0.999 and 9999' represents 'due to limited number of participants with an event, data could not be calculated.'

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

End point timeframe:

Up to approximately 2 years

| **End point values** | Unesbulin and Dacarbazine | Placebo and Dacarbazine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 105 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.87 (0.999 to 9999) | 9999 (9999 to 9999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Treatment-emergent Adverse Events (TEAEs)

| End point title | Number of Participants with Treatment-emergent Adverse Events (TEAEs) |
|---|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. A TEAE was defined as an AE that had an onset date on or after the first dose of study drug until 30 days after last dose or occurred prior to first dose of study drug and worsened in severity after first dose of study drug. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. The safety analysis set included all participants who received at least 1 dose of study drug (unesbulin/placebo or dacarbazine).

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

End point timeframe:

From first dose of study drug up to approximately 2 years

| End point values | Unesbulin and Dacarbazine | Placebo and Dacarbazine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 238 | 120 | | |
| Units: participants | 236 | 112 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to approximately 2 years

Adverse event reporting additional description:

The safety analysis set included all participants who received at least 1 dose of study drug (unesbulin/placebo or dacarbazine).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo and Dacarbazine |

Reporting group description:

Participants received placebo matching to unesbulin tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m^2 IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

| | |
|---|---|
| Reporting group title | Unesbulin and Dacarbazine |

Reporting group description:

Participants received unesbulin 300 mg tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m^2 IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

| Serious adverse events | Placebo and Dacarbazine | Unesbulin and Dacarbazine | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 43 / 120 (35.83%) | 81 / 238 (34.03%) | |
| number of deaths (all causes) | 27 | 49 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 3 / 238 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lung | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 120 (1.67%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disease progression | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 3 / 238 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 3 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Malaise | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| 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** | | | |
| Vaginal haemorrhage | Additional description: This is a sex-specific AE. Only female participants were at risk. | | |
| subjects affected / exposed[1] | 0 / 93 (0.00%) | 1 / 187 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 5 / 238 (2.10%) | |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| 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 | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (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 | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Atrial thrombosis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bundle branch block left | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Central nervous system lesion | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paralysis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurotoxicity | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 120 (2.50%) | 5 / 238 (2.10%) | |
| occurrences causally related to treatment / all | 2 / 3 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 120 (1.67%) | 6 / 238 (2.52%) | |
| occurrences causally related to treatment / all | 2 / 2 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 120 (1.67%) | 4 / 238 (1.68%) | |
| occurrences causally related to treatment / all | 1 / 2 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematotoxicity | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 8 / 238 (3.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bicytopenia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 3 / 238 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 120 (1.67%) | 3 / 238 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Haemoperitoneum | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Subcapsular hepatic haematoma | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| 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 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| COVID-19 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 5 / 238 (2.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pertussis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 3 / 238 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 120 (2.50%) | 4 / 238 (1.68%) | |
| occurrences causally related to treatment / all | 2 / 3 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord infection | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 120 (0.83%) | 2 / 238 (0.84%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a sex-specific AE. Only female participants were at risk.

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

| **Non-serious adverse events** | Placebo and Dacarbazine | Unesbulin and Dacarbazine | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 112 / 120 (93.33%) | 234 / 238 (98.32%) | |
| Investigations | | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | 36 / 238 (15.13%) | |
| occurrences (all) | 20 | 83 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 17 / 120 (14.17%) | 51 / 238 (21.43%) | |
| occurrences (all) | 42 | 114 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 13 / 120 (10.83%) | 60 / 238 (25.21%) | |
| occurrences (all) | 28 | 140 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 13 / 238 (5.46%) | |
| occurrences (all) | 6 | 28 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 8 / 120 (6.67%) | 20 / 238 (8.40%) | |
| occurrences (all) | 10 | 27 | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 10 / 120 (8.33%) | 18 / 238 (7.56%) | |
| occurrences (all) | 13 | 27 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 120 (8.33%) | 32 / 238 (13.45%) | |
| occurrences (all) | 13 | 35 | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 120 (1.67%) | 17 / 238 (7.14%) | |
| occurrences (all) | 2 | 19 | |
| Headache | | | |
| subjects affected / exposed | 14 / 120 (11.67%) | 29 / 238 (12.18%) | |
| occurrences (all) | 16 | 42 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 4 / 120 (3.33%) | 15 / 238 (6.30%) | |
| occurrences (all) | 4 | 21 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 35 / 120 (29.17%) | 103 / 238 (43.28%) | |
| occurrences (all) | 91 | 260 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 27 / 120 (22.50%) | 75 / 238 (31.51%) | |
| occurrences (all) | 76 | 238 | |
| Neutropenia | | | |
| subjects affected / exposed | 23 / 120 (19.17%) | 88 / 238 (36.97%) | |
| occurrences (all) | 53 | 298 | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 120 (5.83%) | 15 / 238 (6.30%) | |
| occurrences (all) | 17 | 81 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 12 / 120 (10.00%) | 27 / 238 (11.34%) | |
| occurrences (all) | 24 | 69 | |
| Fatigue | | | |
| subjects affected / exposed | 44 / 120 (36.67%) | 93 / 238 (39.08%) | |
| occurrences (all) | 51 | 135 | |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | 15 / 238 (6.30%) | |
| occurrences (all) | 10 | 17 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 12 / 120 (10.00%) | 20 / 238 (8.40%) | |
| occurrences (all) | 13 | 22 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 15 / 238 (6.30%) | |
| occurrences (all) | 6 | 19 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 44 / 120 (36.67%) | 115 / 238 (48.32%) | |
| occurrences (all) | 62 | 153 | |
| Diarrhoea | | | |
| subjects affected / exposed | 27 / 120 (22.50%) | 131 / 238 (55.04%) | |
| occurrences (all) | 36 | 216 | |
| Constipation | | | |
| subjects affected / exposed | 19 / 120 (15.83%) | 50 / 238 (21.01%) | |
| occurrences (all) | 23 | 57 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | 13 / 238 (5.46%) | |
| occurrences (all) | 6 | 13 | |
| Vomiting | | | |
| subjects affected / exposed | 17 / 120 (14.17%) | 43 / 238 (18.07%) | |
| occurrences (all) | 20 | 61 | |
| Abdominal pain | | | |
| subjects affected / exposed | 11 / 120 (9.17%) | 42 / 238 (17.65%) | |
| occurrences (all) | 13 | 50 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 10 / 120 (8.33%) | 29 / 238 (12.18%) | |
| occurrences (all) | 12 | 33 | |
| Dyspnoea | | | |
| subjects affected / exposed | 23 / 120 (19.17%) | 26 / 238 (10.92%) | |
| occurrences (all) | 25 | 32 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Insomnia | | | |
| subjects affected / exposed | 4 / 120 (3.33%) | 14 / 238 (5.88%) | |
| occurrences (all) | 4 | 14 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 12 / 120 (10.00%) | 20 / 238 (8.40%) | |
| occurrences (all) | 15 | 23 | |
| Back pain | | | |
| subjects affected / exposed | 13 / 120 (10.83%) | 22 / 238 (9.24%) | |
| occurrences (all) | 15 | 24 | |
| Myalgia | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 19 / 238 (7.98%) | |
| occurrences (all) | 5 | 26 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 8 / 120 (6.67%) | 14 / 238 (5.88%) | |
| occurrences (all) | 8 | 22 | |
| COVID-19 | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | 13 / 238 (5.46%) | |
| occurrences (all) | 9 | 15 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 7 / 120 (5.83%) | 11 / 238 (4.62%) | |
| occurrences (all) | 10 | 12 | |
| Decreased appetite | | | |
| subjects affected / exposed | 14 / 120 (11.67%) | 37 / 238 (15.55%) | |
| occurrences (all) | 16 | 46 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 31 January 2022 | The overall reason for this version of the protocol was to modify the timing and description of the interim analysis for futility and efficacy evaluation. - The lower limit of Grade 1 thrombocytopenia platelet count was changed from 750000 to 75000. - The timing and description of the interim analysis for futility and efficacy evaluation were modified. |
| 28 April 2023 | The overall reason for this version of the protocol was to incorporate comprehensively all modifications requested by country-specific health authorities and Ethics Committees in response to the Clinical Trial Application. Additional updates were made for improved clarity and study conduct. - It was specified that Overall Survival was the key secondary endpoint. Additional details describing the analysis of this key secondary endpoint were added to the Synopsis. - It was clarified that no dose reduction of unesbulin/placebo was permitted. - An exception to Inclusion Criterion was added for participants with Gilbert's syndrome who had elevated bilirubin values. - Inclusion Criterion was modified to increase the eligibility limit for aspartate aminotransferase and alanine aminotransferase from 1.5 to 3 times the upper limit of normal. - It was clarified in Inclusion Criterion that prior lines of treatment may include but were not limited to single-agent doxorubicin or other anthracycline, doxorubicin plus ifosfamide, trabectedin, pazopanib, or gemcitabine with or without docetaxel. - Administration of live vaccines was added as an Exclusion Criterion and as a concomitant medication. - It was clarified that survival follow-up would continue every 3 months as per the Schedule of Assessments. - Treatment-emergent adverse events were defined. |
| 28 November 2023 | The main reasons for this version were to clarify study procedures in cases of DTIC interruption and revise the analysis of the key secondary endpoint (Overall Survival). Additional updates were made to reflect changes in study staff, improved clarity, and to address clerical errors. - It was clarified that a hierarchical testing procedure would be utilized. - For participants who have DTIC interrupted or held, it was added that clinical laboratory assessments would be required weekly for the first 3 weeks after DTIC reintroduction. For subsequent cycles, the clinical laboratory assessments could be performed at a minimum of once per cycle or more frequently per the investigator's discretion to ensure that the participant met the protocol-defined safety criteria. - The following statement was added: "DTIC should be reintroduced at least 48 hours after unesbulin dosing". |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early due to business decision.

Notes: