



Clinical trial results: Defibrotide for Patients with Hepatic Veno-occlusive Disease (VOD): A Treatment IND Study Summary

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|--------------------------|----------------|
| EudraCT number | 2017-004316-18 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 10 July 2016 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 07 August 2020 |
| First version publication date | 07 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 2006-05 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|--------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00628498 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND number: 62,118 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Jazz Pharmaceuticals |
| Sponsor organisation address | 3180 Porter Drive, Palo Alto, United States, |
| Public contact | Clinical Trial Disclosure, Jazz Pharmaceuticals, +1 215832-3750, |
| Scientific contact | Clinical Trial Disclosure, Jazz Pharmaceuticals, +1 215832-3750, |

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? | Yes |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 July 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to provide access to defibrotide as an investigational new drug under an expanded access treatment protocol.

Protection of trial subjects:

Infants, children for whom the parent(s) or legal guardian needed to give consent and the child and Adolescent itself assent as required

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 14 December 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United States: 1154 |
| Worldwide total number of subjects | 1154 |
| EEA total number of subjects | 0 |

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) | 180 |
| Children (2-11 years) | 382 |
| Adolescents (12-17 years) | 151 |
| Adults (18-64 years) | 415 |
| From 65 to 84 years | 26 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult and pediatric patients underwent physical exam/radiography and laboratory tests during the Screening phase of the study to confirm clinical diagnosis of Veno-Occlusive Disease (VOD)/Severe VOD.

Period 1

| | |
|------------------------------|------------------------------------|
| Period 1 title | Safety Population (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|-------------|
| Arm title | Defibrotide |
|-----------|-------------|

Arm description:

Defibrotide 25 mg/kg day given in 4 divided doses approximately every 6 hours

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Defibrotide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

All patients were to receive 25 mg/kg/day of defibrotide.

| Number of subjects in period 1 | Defibrotide |
|--------------------------------|-------------|
| Started | 1154 |
| Completed | 1154 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Defibrotide |
|-----------------------|-------------|

Reporting group description:

Defibrotide 25 mg/kg day given in 4 divided doses approximately every 6 hours

| Reporting group values | Defibrotide | Total | |
|--|-------------|-------|--|
| Number of subjects | 1154 | 1154 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Age at time of HSCT/chemo | | | |
| Units: years | | | |
| arithmetic mean | 19.32 | | |
| standard deviation | ± 20.004 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 503 | 503 | |
| Male | 651 | 651 | |

End points

End points reporting groups

| | |
|---|-------------|
| Reporting group title | Defibrotide |
| Reporting group description: | |
| Defibrotide 25 mg/kg day given in 4 divided doses approximately every 6 hours | |

Primary: Survival by Day+100 Post Stem Cell Transplant or Chemotherapy

| | |
|-----------------|--|
| End point title | Survival by Day+100 Post Stem Cell Transplant or Chemotherapy ^[1] |
|-----------------|--|

End point description:

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

End point timeframe:

Day +100 from HSCT or 100 days from start of chemotherapy

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis performed.

| | | | | |
|---|---------------------|--|--|--|
| End point values | Defibrotide | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 571 | | | |
| Units: Percentage of participants alive | | | | |
| number (confidence interval 95%) | 49.9 (45.8 to 54.0) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety data collected included AEs/SAEs reported through 30 days following the last dose of defibrotide.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Defibrotide |
|-----------------------|-------------|

Reporting group description: -

| Serious adverse events | Defibrotide | | |
|---|---------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 598 / 1154 (51.82%) | | |
| number of deaths (all causes) | 255 | | |
| number of deaths resulting from adverse events | 31 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute lymphocytic leukaemia recurrent | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute myeloid leukaemia recurrent | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 4 | | |

| | | | | |
|---|------------------|--|--|--|
| Burkitt's lymphoma | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Burkitt's lymphoma recurrent | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Leukaemia recurrent | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mantle cell lymphoma | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Myeloid leukaemia | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Neuroblastoma recurrent | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Post transplant lymphoproliferative disorder | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Recurrent cancer | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Rhabdomyosarcoma | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sarcoma | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| T-cell lymphoma recurrent | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Vascular disorders | | | |
| Capillary leak syndrome | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 7 / 1154 (0.61%) | | |
| occurrences causally related to treatment / all | 5 / 8 | | |
| deaths causally related to treatment / all | 2 / 2 | | |
| Haemorrhagic infarction | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 46 / 1154 (3.99%) | | |
| occurrences causally related to treatment / all | 7 / 52 | | |
| deaths causally related to treatment / all | 2 / 10 | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Microangiopathy | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Shock | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Venoocclusive disease | | | |

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|--|---------------------|--|--|
| subjects affected / exposed | 9 / 1154 (0.78%) | | |
| occurrences causally related to treatment / all | 1 / 9 | | |
| deaths causally related to treatment / all | 0 / 6 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disease progression | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Mucosal haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multi-organ disorder | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Multi-organ failure | | | |
| subjects affected / exposed | 139 / 1154 (12.05%) | | |
| occurrences causally related to treatment / all | 3 / 140 | | |
| deaths causally related to treatment / all | 3 / 133 | | |
| Oedema | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumatosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 1154 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Acute graft versus host disease | | | |
| subjects affected / exposed | 6 / 1154 (0.52%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| Acute graft versus host disease in intestine | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute graft versus host disease in liver | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute graft versus host disease in skin | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Engraftment syndrome | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-------------------|--|--|
| Graft versus host disease | | | |
| subjects affected / exposed | 15 / 1154 (1.30%) | | |
| occurrences causally related to treatment / all | 0 / 15 | | |
| deaths causally related to treatment / all | 0 / 10 | | |
| Graft versus host disease in intestine | | | |
| subjects affected / exposed | 6 / 1154 (0.52%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Graft versus host disease in liver | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Graft versus host disease in skin | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 16 / 1154 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 17 | | |
| deaths causally related to treatment / all | 0 / 13 | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Alveolar proteinosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Apnoea | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-------------------|--|--|--|
| Atelectasis | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Bronchial haemorrhage | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Diffuse alveolar damage | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epistaxis | | | | |
| subjects affected / exposed | 7 / 1154 (0.61%) | | | |
| occurrences causally related to treatment / all | 4 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemothorax | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoxia | | | | |
| subjects affected / exposed | 31 / 1154 (2.69%) | | | |
| occurrences causally related to treatment / all | 1 / 31 | | | |
| deaths causally related to treatment / all | 1 / 11 | | | |
| Idiopathic pneumonia syndrome | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 6 / 1154 (0.52%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Laryngeal stenosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infiltration | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pleural haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary alveolar haemorrhage | | | |
| subjects affected / exposed | 13 / 1154 (1.13%) | | |
| occurrences causally related to treatment / all | 8 / 14 | | |
| deaths causally related to treatment / all | 2 / 6 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 57 / 1154 (4.94%) | | |
| occurrences causally related to treatment / all | 44 / 60 | | |
| deaths causally related to treatment / all | 11 / 18 | | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 6 / 1154 (0.52%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary veno-occlusive disease | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory arrest | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 22 / 1154 (1.91%) | | |
| occurrences causally related to treatment / all | 1 / 22 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 80 / 1154 (6.93%) | | |
| occurrences causally related to treatment / all | 4 / 84 | | |
| deaths causally related to treatment / all | 3 / 39 | | |
| Tachypnoea | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|------------------|--|--|--|
| Alanine aminotransferase increased | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspartate aminotransferase increased | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood bilirubin increased | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Blood creatine increased | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gamma-glutamyltransferase increased | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Human herpes virus 6 serology positive | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| International normalised ratio increased | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oxygen saturation decreased | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|------------------|--|--|--|
| Pulse absent | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transaminases increased | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urine output decreased | | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Weight increased | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Injury, poisoning and procedural complications | | | | |
| Brain herniation | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Endotracheal intubation complication | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Engraft failure | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Feeding tube complication | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|-------------------|--|--|--|
| Hepatic haematoma | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Overdose | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Post procedural haemorrhage | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative thoracic procedure complication | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Procedural complication | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Procedural haemorrhage | | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 1 / 2 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 32 / 1154 (2.77%) | | | |
| occurrences causally related to treatment / all | 0 / 33 | | | |
| deaths causally related to treatment / all | 0 / 27 | | | |
| Subdural haematoma | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subdural haemorrhage | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tracheal haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transfusion-related acute lung injury | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transplant failure | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 8 / 1154 (0.69%) | | |
| occurrences causally related to treatment / all | 2 / 8 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block complete | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Bradycardia | | | |
| subjects affected / exposed | 6 / 1154 (0.52%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 13 / 1154 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 15 | | |
| deaths causally related to treatment / all | 0 / 6 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 1 / 3 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 9 / 1154 (0.78%) | | |
| occurrences causally related to treatment / all | 0 / 9 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiopulmonary failure | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 8 / 1154 (0.69%) | | |
| occurrences causally related to treatment / all | 2 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Right ventricular failure | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Torsade de pointes | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Autonomic neuropathy | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain hypoxia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain injury | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Brain oedema | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Central nervous system haemorrhage | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebellar haematoma | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cerebral haemorrhage | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Cerebral infarction | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cerebral ischaemia | | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Convulsion | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 5 / 1154 (0.43%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Depressed level of consciousness | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Encephalopathy | | | | |
| subjects affected / exposed | 9 / 1154 (0.78%) | | | |
| occurrences causally related to treatment / all | 1 / 10 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Facial nerve disorder | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhage intracranial | | | | |
| subjects affected / exposed | 6 / 1154 (0.52%) | | | |
| occurrences causally related to treatment / all | 5 / 6 | | | |
| deaths causally related to treatment / all | 3 / 4 | | | |
| Hepatic encephalopathy | | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Hydrocephalus | | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypertonia | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intraventricular haemorrhage | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coagulopathy | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 1 / 3 | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Febrile neutropenia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 6 / 1154 (0.52%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemolysis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Histiocytosis haematophagic | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombotic thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Eye disorders | | | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | | |
|---|------------------|--|--|--|
| Abdominal compartment syndrome | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal distension | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal pain | | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Ascites | | | | |
| subjects affected / exposed | 7 / 1154 (0.61%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 9 / 1154 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 9 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea haemorrhagic | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric haemorrhage | | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 8 / 1154 (0.69%) | | |
| occurrences causally related to treatment / all | 6 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 33 / 1154 (2.86%) | | |
| occurrences causally related to treatment / all | 26 / 37 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Haematemesis | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Intra-abdominal haemorrhage | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritoneal haemorrhage | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Retroperitoneal haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 4 / 1154 (0.35%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malabsorption | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatic failure | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 19 / 1154 (1.65%) | | |
| occurrences causally related to treatment / all | 0 / 19 | | |
| deaths causally related to treatment / all | 0 / 17 | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Hepatorenal failure | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatorenal syndrome | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Venoocclusive liver disease | | | |
| subjects affected / exposed | 87 / 1154 (7.54%) | | |
| occurrences causally related to treatment / all | 1 / 88 | | |
| deaths causally related to treatment / all | 1 / 86 | | |
| Skin and subcutaneous tissue disorders | | | |
| Haemorrhage subcutaneous | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 6 / 1154 (0.52%) | | |
| occurrences causally related to treatment / all | 2 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Renal failure | | | |
| subjects affected / exposed | 45 / 1154 (3.90%) | | |
| occurrences causally related to treatment / all | 0 / 45 | | |
| deaths causally related to treatment / all | 0 / 16 | | |
| Renal failure acute | | | |
| subjects affected / exposed | 22 / 1154 (1.91%) | | |
| occurrences causally related to treatment / all | 1 / 22 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Renal impairment | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary retention | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urogenital haemorrhage | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myopathy | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acid fast bacilli infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenovirus infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|------------------|--|--|--|
| Appendicitis | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspergillosis | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| BK virus infection | | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Bacteraemia | | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacterial sepsis | | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Burkholderia cepacia complex infection | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Candida sepsis | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cerebral fungal infection | | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Citrobacter sepsis | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Corona virus infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Device related infection | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterobacter bacteraemia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterobacter infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterococcal infection | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterococcal sepsis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fungal sepsis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatitis viral | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Human herpesvirus 6 infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection | | | |
| subjects affected / exposed | 17 / 1154 (1.47%) | | |
| occurrences causally related to treatment / all | 0 / 17 | | |
| deaths causally related to treatment / all | 0 / 8 | | |
| Lobar pneumonia | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 7 / 1154 (0.61%) | | |
| occurrences causally related to treatment / all | 1 / 7 | | |
| deaths causally related to treatment / all | 1 / 3 | | |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 14 / 1154 (1.21%) | | |
| occurrences causally related to treatment / all | 0 / 14 | | |
| deaths causally related to treatment / all | 0 / 9 | | |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 4 / 1154 (0.35%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Pneumonia parainfluenzae viral | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pseudomonal bacteraemia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Septic embolus | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Septic shock | | | |
| subjects affected / exposed | 8 / 1154 (0.69%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 8 | | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stenotrophomonas sepsis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Systemic candida | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Toxoplasmosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicella | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Zygomycosis | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Alkalosis | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Fluid overload | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hyperammonaemia | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 1154 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 5 / 1154 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 6 / 1154 (0.52%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1154 (0.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 2 / 1154 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |

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

| | | | |
|---|---------------------|--|--|
| Non-serious adverse events | Defibrotide | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 166 / 1154 (14.38%) | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 93 / 1154 (8.06%) | | |
| occurrences (all) | 126 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 70 / 1154 (6.07%) | | |
| occurrences (all) | 84 | | |
| Vomiting | | | |
| subjects affected / exposed | 63 / 1154 (5.46%) | | |
| occurrences (all) | 82 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 17 December 2007 | <ul style="list-style-type: none">• Clarified that AEs and outcome data were to be collected on Day+30 and Day+100 post-HSCT.• Included additional information related to recording of AEs recording, including details on relationship to study drug.• Updated criteria used to define complete response (CR). |
| 12 August 2009 | <ul style="list-style-type: none">• Modified the eligibility criteria by removing the requirement for patients to demonstrate MOF prior to enrollment and to be eligible only following HSCT - patients could meet eligibility criteria following chemotherapy.• The requirement for VOD before Day+35 and MOF (as applicable) by Day+45 was removed allowing patients with late onset VOD to be treated.• Clarified the duration of treatment to allow continued treatment until the patient achieved a CR or until hospital discharge.• Hemodynamic instability was modified to include the requirement for 2 or more pressors (not including renal doses of dopamine).• Discontinuation criteria were modified to permit patients who required multiple pressors after defibrotide to continue on defibrotide. (As long as the patient could maintain his/her mean arterial pressure within 1 standard deviation of age-adjusted controls).• Introduced a cost recovery program. |
| 11 August 2010 | <ul style="list-style-type: none">• Introduced a new formulation (paraben preservatives removed, glass vials instead of glass ampoules) and container closure system for defibrotide.• Reintroduced the comparison of the Historical Control arm of the Phase 3 study 2005-01 and the patients enrolled under Protocol 2006-05 who met eligibility criteria of Protocol 2005-01, regarding Day+100 survival and CR (Note: this analysis had been removed in Amendment 2 when entry criteria were broadened).• Included a reporting window of ± 3 days and ± 7 days for Day+30 and Day+100 assessments, respectively.• Allowed an increased number of enrolled patients (from 100-200 to 200-300 patients). |
| 31 March 2011 | <ul style="list-style-type: none">• Added pregnancy to the contraindications to the use of defibrotide. |
| 21 August 2012 | <p>Allowed enrollment of patients with a VOD diagnosis based on modified Seattle Criteria, in addition to those fulfilling Baltimore criteria (elevation of total bilirubin to 2.0 mg/dL or higher was no longer mandatory).</p> <ul style="list-style-type: none">• Increased the number of enrolled patients (from 200-300 patients to approximately 600 patients). |
| 29 August 2014 | <ul style="list-style-type: none">• Increased the number of patients to be enrolled (from 600 to 1000).• Changed the end of treatment with defibrotide from achievement of CR or until discharge from the hospital to until signs and symptoms of VOD resolved.• Removed comparison to historical control from Protocol 2005-01.• Added disallowance of any medication that increased the risk of hemorrhage.• Changed exclusion criterion regarding hemodynamic stability to include a recommendation for adult patients.• Added option of contact without return visit to clinic for follow-up at Day +30 and Day +100 post-HSCT.• Widened the acceptable concentration range for defibrotide solution for infusion due to new stability data. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported