



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

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 <sup>[1]</sup>
-----------------	--

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.

<b>End point values</b>	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			

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		

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		

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 %

<b>Non-serious adverse events</b>	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"><li>• Clarified that AEs and outcome data were to be collected on Day+30 and Day+100 post-HSCT.</li><li>• Included additional information related to recording of AEs recording, including details on relationship to study drug.</li><li>• Updated criteria used to define complete response (CR).</li></ul>
12 August 2009	<ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li><li>• Clarified the duration of treatment to allow continued treatment until the patient achieved a CR or until hospital discharge.</li><li>• Hemodynamic instability was modified to include the requirement for 2 or more pressors (not including renal doses of dopamine).</li><li>• 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).</li><li>• Introduced a cost recovery program.</li></ul>
11 August 2010	<ul style="list-style-type: none"><li>• Introduced a new formulation (paraben preservatives removed, glass vials instead of glass ampoules) and container closure system for defibrotide.</li><li>• 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).</li><li>• Included a reporting window of <math>\pm 3</math> days and <math>\pm 7</math> days for Day+30 and Day+100 assessments, respectively.</li><li>• Allowed an increased number of enrolled patients (from 100-200 to 200-300 patients).</li></ul>
31 March 2011	<ul style="list-style-type: none"><li>• Added pregnancy to the contraindications to the use of defibrotide.</li></ul>
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"><li>• Increased the number of enrolled patients (from 200-300 patients to approximately 600 patients).</li></ul>
29 August 2014	<ul style="list-style-type: none"><li>• Increased the number of patients to be enrolled (from 600 to 1000).</li><li>• 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.</li><li>• Removed comparison to historical control from Protocol 2005-01.</li><li>• Added disallowance of any medication that increased the risk of hemorrhage.</li><li>• Changed exclusion criterion regarding hemodynamic stability to include a recommendation for adult patients.</li><li>• Added option of contact without return visit to clinic for follow-up at Day +30 and Day +100 post-HSCT.</li><li>• Widened the acceptable concentration range for defibrotide solution for infusion due to new stability data.</li></ul>

Notes:

---

## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported