Clinical trial results:
A Phase 3, Randomized, Adaptive Study Comparing the Efficacy and Safety of Defibrotide vs Best Supportive Care in the Prevention of Hepatic Veno-Occlusive Disease in Adult and Pediatric Patients Undergoing Hematopoietic Stem Cell Transplant

Summary

EudraCT number	2016-002004-10
Trial protocol	ES GB BE DE FR IT
Global end of trial date	20 October 2020

Results information

Result version number	v1 (current)
This version publication date	06 May 2021
First version publication date	06 May 2021

Trial information

Trial identification

Sponsor protocol code	15-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02851407
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 62,118

Notes:

Sponsors

Sponsor organisation name	Jazz Pharmaceuticals Inc.
Sponsor organisation address	3170 Porter Drive, Palo Alto, United States, 94304
Public contact	Director, Clinical Trial Disclosure & Transparency, Jazz Pharmaceuticals, Inc., +1 2158709177, ClinicalTrialDisclosure@JazzPharma.com
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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 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 October 2020
Global end of trial reached?	Yes
Global end of trial date	20 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the efficacy of defibrotide vs Best Supportive Care for the prevention of Veno-Occlusive Disease (VOD) as measured by VOD-free survival by Day +30 post-hematopoietic stem cell transplant (HSCT) in participants who are at high risk or very high risk for developing VOD.

Protection of trial subjects:

All participants provided their written informed consent or assent, as applicable, before any study-related procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Turkey: 24
Country: Number of subjects enrolled	United States: 106
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Japan: 48
Country: Number of subjects enrolled	New Zealand: 2
Worldwide total number of subjects	372
EEA total number of subjects	110

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)	34
Children (2-11 years)	135
Adolescents (12-17 years)	38
Adults (18-64 years)	149
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants, their parents/legal guardians, or representatives were required to sign a statement of informed consent.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Defibrotide

Arm description:

Eligible participants were randomly assigned to receive Defibrotide in addition to best supportive care.

Arm type	Experimental
Investigational medicinal product name	Defibrotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously at a dose of 25 mg/kg/day in addition to best supportive care within 24 hours prior to the start of the first dose of the conditioning regimen and continued (for those participants without a VOD diagnosis) for a recommended minimum of 21 days and end no later than Day +30 post HSCT.

Arm title	Best Supportive Care

Arm description:

Eligible participants were randomly assigned to receive best supportive care alone.

Arm type	Reference therapy
Investigational medicinal product name	Best Supportive Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Best supportive care alone (without the addition of defibrotide) according to institutional guidelines and participant need, was administered on the first day of conditioning and continued until Day +30 post HSCT or hospital discharge, whichever was sooner, or diagnosis of VOD, if applicable.

Number of subjects in period 1	Defibrotide	Best Supportive Care
Started	190	182
Completed	120	121
Not completed	70	61
Adverse event, serious fatal	6	8
Physician decision	7	6
Enrolled in an investigational study	-	1
Transferred to hospital closer to home	-	1
Disease relapse	9	6
Screen failure	2	1
Withdrawal by parent/guardian	2	7
Transferred to another hospital to continue	1	-
Consent withdrawn by subject	5	3
Adverse event, non-fatal	7	5
Early recovery	1	-
Lost to follow-up	-	2
Other Death	30	20
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Defibrotide
Reporting group description:	
Eligible participants were randomly assigned to receive Defibrotide in addition to best supportive care.	
Reporting group title	Best Supportive Care
Reporting group description:	
Eligible participants were randomly assigned to receive best supportive care alone.	

Reporting group values	Defibrotide	Best Supportive Care	Total
Number of subjects	190	182	372
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	22.7	23.2	
standard deviation	± 21.87	± 21.73	-
Gender categorical Units: Subjects			
Female	90	82	172
Male	100	100	200

End points

End points reporting groups

Reporting group title	Defibrotide
Reporting group description:	
Eligible participants were randomly assigned to receive Defibrotide in addition to best supportive care.	
Reporting group title	Best Supportive Care
Reporting group description:	
Eligible participants were randomly assigned to receive best supportive care alone.	

Primary: Number of Participants Experiencing Veno-occlusive Disease (VOD)-Free Survival by Day +30 Post-Hematopoietic Stem Cell Transplant (HSCT)

End point title	Number of Participants Experiencing Veno-occlusive Disease (VOD)-Free Survival by Day +30 Post-Hematopoietic Stem Cell Transplant (HSCT)
End point description:	
End point type	Primary
End point timeframe:	
Day +30 post-HSCT	

End point values	Defibrotide	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	182		
Units: number of participants with No VOD/Death	112	113		

Statistical analyses

Statistical analysis title	P-value from log rank statistics
Statistical analysis description:	
P-value was calculated for the combined Stage 1 and Stage 2 log rank statistics stratified by risk status and age group using the method described by Cui, Hung, and Wang (1999).	
Comparison groups	Best Supportive Care v Defibrotide
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8504
Method	Logrank

Secondary: Number of Participants Experiencing VOD-Free survival by Day +100 post HSCT

End point title	Number of Participants Experiencing VOD-Free survival by Day +100 post HSCT

End point description:

End point type	Secondary

End point timeframe:

Day +100 Post-HSCT

End point values	Defibrotide	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	182		
Units: number of participants with No VOD/Death	74	81		

Statistical analyses

Statistical analysis title	P-value from log rank statistics

Statistical analysis description:

Based on the pre-planned hierarchical testing strategy, the key secondary efficacy endpoint hypothesis was not evaluated because the primary endpoint was not met. P-values are nominal.

Comparison groups	Defibrotide v Best Supportive Care
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8156
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were reported from date of consent through the end of protocol-specific reporting period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Defibrotide

Reporting group description:

Defibrotide is administered intravenously at a dose of 25 mg/kg/day in addition to best supportive care within 24 hours prior to the first dose of conditioning regimen and will continued (for those patients without a VOD diagnosis) for a recommended minimum of 21 days and end no later than Day +30 post HSCT.

Reporting group title	Best Supportive Care

Reporting group description:

Best supportive care alone (without the addition of defibrotide) according to institutional guidelines and patient need, is administered on the first day of conditioning and will continue until Day +30 post HSCT or hospital discharge, whichever is sooner, or diagnosis of VOD, if applicable.

Serious adverse events	Defibrotide	Best Supportive Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 181 (45.30%)	74 / 174 (42.53%)	
number of deaths (all causes)	35	29	
number of deaths resulting from adverse events	22	18	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myeloid leukaemia recurrent			

subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Burkitt's lymphoma			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukaemia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukaemia recurrent			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Air embolism			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Capillary leak syndrome			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 181 (1.66%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive disease			
subjects affected / exposed	9 / 181 (4.97%)	5 / 174 (2.87%)	
occurrences causally related to treatment / all	0 / 11	1 / 5	
deaths causally related to treatment / all	0 / 4	1 / 2	
Immune system disorders			
Acute graft versus host disease in intestine			
subjects affected / exposed	3 / 181 (1.66%)	4 / 174 (2.30%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute graft versus host disease in liver			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute graft versus host disease in skin			
subjects affected / exposed	4 / 181 (2.21%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	4 / 181 (2.21%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pneumonia syndrome			

subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngospasm			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			

subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 181 (0.55%)	3 / 174 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	6 / 181 (3.31%)	6 / 174 (3.45%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 3	
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper airway obstruction			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 181 (0.55%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus test positive			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus test positive			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella test positive			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Norovirus test positive			

subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Airway complication of anaesthesia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis postoperative			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed engraftment			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Engraft failure			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			

subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebellar haemorrhage			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Headache			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			

subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Presyncope			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 181 (1.66%)	3 / 174 (1.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	3 / 181 (1.66%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	2 / 181 (1.10%)	3 / 174 (1.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anal inflammation			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 181 (0.00%)	5 / 174 (2.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 181 (1.66%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	2 / 181 (1.10%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 181 (0.55%)	3 / 174 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal haemorrhage			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 181 (1.66%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Pneumatosis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	10 / 181 (5.52%)	14 / 174 (8.05%)	
occurrences causally related to treatment / all	0 / 11	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			

subjects affected / exposed	2 / 181 (1.10%)	4 / 174 (2.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 181 (1.66%)	4 / 174 (2.30%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anuria			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 181 (1.10%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			

subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular dysfunction			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 181 (0.55%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
BK virus infection			
subjects affected / exposed	2 / 181 (1.10%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Candida sepsis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis viral			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	2 / 181 (1.10%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 181 (1.10%)	3 / 174 (1.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			

subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 181 (0.00%)	4 / 174 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pseudomonal sepsis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 181 (3.31%)	5 / 174 (2.87%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Septic shock			
subjects affected / exposed	2 / 181 (1.10%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin candida			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 181 (0.55%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 181 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 181 (0.00%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 181 (1.10%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 181 (1.10%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Defibrotide	Best Supportive Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	180 / 181 (99.45%)	174 / 174 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	71 / 181 (39.23%)	55 / 174 (31.61%)	
occurrences (all)	92	80	
Hypotension			
subjects affected / exposed	28 / 181 (15.47%)	26 / 174 (14.94%)	
occurrences (all)	30	32	
Venoocclusive disease			
subjects affected / exposed	8 / 181 (4.42%)	20 / 174 (11.49%)	
occurrences (all)	8	21	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 181 (5.52%)	7 / 174 (4.02%)	
occurrences (all)	11	7	
Chills			
subjects affected / exposed	11 / 181 (6.08%)	14 / 174 (8.05%)	
occurrences (all)	16	16	
Face oedema			
subjects affected / exposed	10 / 181 (5.52%)	12 / 174 (6.90%)	
occurrences (all)	10	16	
Fatigue			
subjects affected / exposed	24 / 181 (13.26%)	23 / 174 (13.22%)	
occurrences (all)	35	28	
Malaise			
subjects affected / exposed	7 / 181 (3.87%)	11 / 174 (6.32%)	
occurrences (all)	12	16	
Oedema peripheral			
subjects affected / exposed	27 / 181 (14.92%)	30 / 174 (17.24%)	
occurrences (all)	33	38	
Pain			
subjects affected / exposed	22 / 181 (12.15%)	19 / 174 (10.92%)	
occurrences (all)	24	20	
Pyrexia			

subjects affected / exposed	113 / 181 (62.43%)	113 / 174 (64.94%)	
occurrences (all)	201	202	
Immune system disorders			
Acute graft versus host disease in intestine			
subjects affected / exposed	13 / 181 (7.18%)	19 / 174 (10.92%)	
occurrences (all)	15	19	
Acute graft versus host disease in skin			
subjects affected / exposed	31 / 181 (17.13%)	34 / 174 (19.54%)	
occurrences (all)	39	41	
Engraftment syndrome			
subjects affected / exposed	14 / 181 (7.73%)	15 / 174 (8.62%)	
occurrences (all)	14	15	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 181 (13.26%)	23 / 174 (13.22%)	
occurrences (all)	29	26	
Dyspnoea			
subjects affected / exposed	12 / 181 (6.63%)	11 / 174 (6.32%)	
occurrences (all)	15	11	
Epistaxis			
subjects affected / exposed	41 / 181 (22.65%)	46 / 174 (26.44%)	
occurrences (all)	52	68	
Hypoxia			
subjects affected / exposed	13 / 181 (7.18%)	10 / 174 (5.75%)	
occurrences (all)	15	10	
Nasal congestion			
subjects affected / exposed	10 / 181 (5.52%)	4 / 174 (2.30%)	
occurrences (all)	13	4	
Oropharyngeal pain			
subjects affected / exposed	20 / 181 (11.05%)	20 / 174 (11.49%)	
occurrences (all)	21	26	
Pleural effusion			
subjects affected / exposed	15 / 181 (8.29%)	7 / 174 (4.02%)	
occurrences (all)	16	9	
Tachypnoea			

subjects affected / exposed	10 / 181 (5.52%)	8 / 174 (4.60%)	
occurrences (all)	10	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	14 / 181 (7.73%)	19 / 174 (10.92%)	
occurrences (all)	14	20	
Depression			
subjects affected / exposed	11 / 181 (6.08%)	3 / 174 (1.72%)	
occurrences (all)	11	4	
Insomnia			
subjects affected / exposed	17 / 181 (9.39%)	31 / 174 (17.82%)	
occurrences (all)	19	35	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	17 / 181 (9.39%)	13 / 174 (7.47%)	
occurrences (all)	33	33	
Alanine aminotransferase increased			
subjects affected / exposed	18 / 181 (9.94%)	28 / 174 (16.09%)	
occurrences (all)	31	48	
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 181 (8.29%)	28 / 174 (16.09%)	
occurrences (all)	31	50	
Blood bilirubin increased			
subjects affected / exposed	26 / 181 (14.36%)	20 / 174 (11.49%)	
occurrences (all)	61	36	
Blood creatinine increased			
subjects affected / exposed	10 / 181 (5.52%)	11 / 174 (6.32%)	
occurrences (all)	25	16	
Cytomegalovirus test positive			
subjects affected / exposed	16 / 181 (8.84%)	9 / 174 (5.17%)	
occurrences (all)	19	15	
International normalised ratio increased			
subjects affected / exposed	10 / 181 (5.52%)	12 / 174 (6.90%)	
occurrences (all)	22	16	
Lymphocyte count decreased			

subjects affected / exposed	6 / 181 (3.31%)	10 / 174 (5.75%)	
occurrences (all)	13	24	
Neutrophil count decreased			
subjects affected / exposed	19 / 181 (10.50%)	25 / 174 (14.37%)	
occurrences (all)	42	74	
Platelet count decreased			
subjects affected / exposed	34 / 181 (18.78%)	43 / 174 (24.71%)	
occurrences (all)	168	161	
Weight decreased			
subjects affected / exposed	5 / 181 (2.76%)	11 / 174 (6.32%)	
occurrences (all)	10	14	
Weight increased			
subjects affected / exposed	22 / 181 (12.15%)	17 / 174 (9.77%)	
occurrences (all)	33	21	
White blood cell count decreased			
subjects affected / exposed	22 / 181 (12.15%)	17 / 174 (9.77%)	
occurrences (all)	41	68	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	15 / 181 (8.29%)	12 / 174 (6.90%)	
occurrences (all)	20	16	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	37 / 181 (20.44%)	24 / 174 (13.79%)	
occurrences (all)	47	30	
Nervous system disorders			
Headache			
subjects affected / exposed	50 / 181 (27.62%)	36 / 174 (20.69%)	
occurrences (all)	77	60	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	50 / 181 (27.62%)	52 / 174 (29.89%)	
occurrences (all)	163	158	
Febrile neutropenia			
subjects affected / exposed	52 / 181 (28.73%)	59 / 174 (33.91%)	
occurrences (all)	57	70	

Leukopenia			
subjects affected / exposed	5 / 181 (2.76%)	10 / 174 (5.75%)	
occurrences (all)	9	22	
Neutropenia			
subjects affected / exposed	31 / 181 (17.13%)	27 / 174 (15.52%)	
occurrences (all)	52	44	
Thrombocytopenia			
subjects affected / exposed	31 / 181 (17.13%)	27 / 174 (15.52%)	
occurrences (all)	56	77	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	17 / 181 (9.39%)	4 / 174 (2.30%)	
occurrences (all)	21	4	
Abdominal pain			
subjects affected / exposed	57 / 181 (31.49%)	48 / 174 (27.59%)	
occurrences (all)	87	70	
Abdominal pain upper			
subjects affected / exposed	12 / 181 (6.63%)	11 / 174 (6.32%)	
occurrences (all)	16	11	
Constipation			
subjects affected / exposed	40 / 181 (22.10%)	39 / 174 (22.41%)	
occurrences (all)	44	40	
Diarrhoea			
subjects affected / exposed	110 / 181 (60.77%)	108 / 174 (62.07%)	
occurrences (all)	176	178	
Haemorrhoids			
subjects affected / exposed	12 / 181 (6.63%)	13 / 174 (7.47%)	
occurrences (all)	14	15	
Nausea			
subjects affected / exposed	109 / 181 (60.22%)	101 / 174 (58.05%)	
occurrences (all)	166	149	
Oral pain			
subjects affected / exposed	13 / 181 (7.18%)	8 / 174 (4.60%)	
occurrences (all)	14	10	
Proctalgia			

subjects affected / exposed	7 / 181 (3.87%)	9 / 174 (5.17%)	
occurrences (all)	8	11	
Stomatitis			
subjects affected / exposed	105 / 181 (58.01%)	114 / 174 (65.52%)	
occurrences (all)	167	188	
Vomiting			
subjects affected / exposed	106 / 181 (58.56%)	91 / 174 (52.30%)	
occurrences (all)	208	179	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	21 / 181 (11.60%)	11 / 174 (6.32%)	
occurrences (all)	26	13	
Erythema			
subjects affected / exposed	13 / 181 (7.18%)	14 / 174 (8.05%)	
occurrences (all)	15	16	
Pruritus			
subjects affected / exposed	13 / 181 (7.18%)	24 / 174 (13.79%)	
occurrences (all)	14	26	
Pruritus generalised			
subjects affected / exposed	13 / 181 (7.18%)	11 / 174 (6.32%)	
occurrences (all)	17	13	
Rash			
subjects affected / exposed	32 / 181 (17.68%)	20 / 174 (11.49%)	
occurrences (all)	43	26	
Rash generalised			
subjects affected / exposed	12 / 181 (6.63%)	6 / 174 (3.45%)	
occurrences (all)	13	8	
Rash maculo-papular			
subjects affected / exposed	13 / 181 (7.18%)	12 / 174 (6.90%)	
occurrences (all)	15	16	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 181 (4.42%)	14 / 174 (8.05%)	
occurrences (all)	11	18	
Haematuria			

subjects affected / exposed	21 / 181 (11.60%)	13 / 174 (7.47%)	
occurrences (all)	23	17	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 181 (3.31%)	10 / 174 (5.75%)	
occurrences (all)	9	11	
Back pain			
subjects affected / exposed	18 / 181 (9.94%)	8 / 174 (4.60%)	
occurrences (all)	20	8	
Pain in extremity			
subjects affected / exposed	19 / 181 (10.50%)	15 / 174 (8.62%)	
occurrences (all)	25	18	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	26 / 181 (14.36%)	23 / 174 (13.22%)	
occurrences (all)	29	24	
Cytomegalovirus viraemia			
subjects affected / exposed	6 / 181 (3.31%)	9 / 174 (5.17%)	
occurrences (all)	7	9	
Device related infection			
subjects affected / exposed	15 / 181 (8.29%)	9 / 174 (5.17%)	
occurrences (all)	17	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	51 / 181 (28.18%)	51 / 174 (29.31%)	
occurrences (all)	75	72	
Fluid overload			
subjects affected / exposed	13 / 181 (7.18%)	8 / 174 (4.60%)	
occurrences (all)	16	12	
Fluid retention			
subjects affected / exposed	14 / 181 (7.73%)	16 / 174 (9.20%)	
occurrences (all)	15	18	
Hyperglycaemia			
subjects affected / exposed	22 / 181 (12.15%)	17 / 174 (9.77%)	
occurrences (all)	31	35	
Hyperkalaemia			

subjects affected / exposed	12 / 181 (6.63%)	12 / 174 (6.90%)	
occurrences (all)	16	18	
Hypoalbuminaemia			
subjects affected / exposed	29 / 181 (16.02%)	23 / 174 (13.22%)	
occurrences (all)	60	55	
Hypocalcaemia			
subjects affected / exposed	19 / 181 (10.50%)	24 / 174 (13.79%)	
occurrences (all)	28	48	
Hypokalaemia			
subjects affected / exposed	75 / 181 (41.44%)	63 / 174 (36.21%)	
occurrences (all)	114	111	
Hypomagnesaemia			
subjects affected / exposed	71 / 181 (39.23%)	59 / 174 (33.91%)	
occurrences (all)	123	123	
Hyponatraemia			
subjects affected / exposed	17 / 181 (9.39%)	13 / 174 (7.47%)	
occurrences (all)	24	19	
Hypophosphataemia			
subjects affected / exposed	20 / 181 (11.05%)	23 / 174 (13.22%)	
occurrences (all)	34	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2017	Changes to master ICF (Version 2), Assent Form 7-9 years of age (Version 2), Assent Form 10-12 years of age (Version 2), Assent Form 13-15 years of age (Version 2), Parent Information Sheet and ICF (Version 2), Intensive Pharmacokinetic Testing Consent (Version 2). Protocol 15-007 Data Monitoring Committee (DMC) Charter (Version 2).
24 February 2017	Changes to master ICF (Version 3), Assent Form 7-9 years of age (Version 3), Assent Form 10-12 years of age (Version 3), Assent Form 13-15 years of age (Version 3), Parent Information Sheet and ICF (Version 3 and 3.1), Intensive Pharmacokinetic Testing Consent (Version 3). Protocol 15-007 Data Monitoring Committee (DMC) Charter (Version 3).
20 August 2018	Changes to master ICF (Version 4), Assent Form 7-9 years of age (Version 4), Assent Form 10-12 years of age (Version 4), Assent Form 13-15 years of age (Version 4), Parent Information Sheet and ICF (Version 4), Intensive Pharmacokinetic Testing Consent (Version 4).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported