Clinical trial results:
A Phase 2, Prospective, Randomized, Open-label Study on the Efficacy of Defibrotide Added to Standard of Care Immunoprophylaxis for the Prevention of Acute Graft-versus-Host-Disease in Adult and Pediatric Patients After Allogeneic Hematopoietic Stem Cell Transplant

Summary

EudraCT number	2017-003309-16
Trial protocol	DE ES GB IT BE PT AT GR BG PL HR
Global end of trial date	12 May 2020

Results information

Result version number	v1 (current)
This version publication date	18 April 2021
First version publication date	18 April 2021

Trial information

Trial identification

Sponsor protocol code	JZP963-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03339297
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., 215 8709177, ClinicalTrialDisclosure@jazzpharma.com
Scientific contact	Director, Clinical Trial Disclosure & Transparency, Jazz Pharmaceuticals, Inc., 215 8709177, ClinicalTrialDisclosure@jazzpharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2020
Global end of trial reached?	Yes
Global end of trial date	12 May 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 added to standard of care immunoprophylaxis vs standard of care (SoC) mmunoprophylaxis alone.

Protection of trial subjects:

Written informed consent and/or assent were obtained before any study procedure were performed in the study and the date of the written consent was obtained and documented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2018
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	Spain: 14
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 68
Worldwide total number of subjects	152
EEA total number of subjects	83

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)	3
Children (2-11 years)	3
Adolescents (12-17 years)	1
Adults (18-64 years)	119
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Informed consent and/or assent was obtained from participants, parents/legal guardians or representatives.

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 Prophylaxis

Arm description:

Eligible participants were randomly assigned to receive defibrotide prophylaxis.

Arm type	Experimental
Investigational medicinal product name	Defibrotide Prophylaxis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Defibrotide solution was administered intravenously by study site personnel at a dose of 25 mg/kg/day.

Arm title	Standard of Care (SOC)

Arm description:

Eligible participants were randomly assigned to receive SoC immunoprophylaxis alone in a 1:1 ratio.

Arm type	Active comparator
Investigational medicinal product name	SOC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Standard of care was administered according to local institutional guidelines, physician preference, and participant need.

Number of subjects in period 1	Defibrotide Prophylaxis	Standard of Care (SOC)
Started	79	73
Completed	56	59
Not completed	23	14
Adverse event, serious fatal	-	2

Physician decision	1	1
Relapse of disease new transplant performed	1	-
Disease relapse	2	-
Hepatic candidosis	1	-
Consent withdrawn by subject	3	3
Patient was not eligible	1	-
Adverse event, non-fatal	1	-
Death	10	7
Early termination, did not proceed to transplant	1	-
Patient relapsed and did not proceed to transplant	-	1
Relapse of hematologic disease	1	-
Problems with donor and diagnosis of early relapse	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Defibrotide Prophylaxis
Reporting group description:	
Eligible participants were randomly assigned to receive defibrotide prophylaxis.	
Reporting group title	Standard of Care (SOC)
Reporting group description:	
Eligible participants were randomly assigned to receive SoC immunoprophylaxis alone in a 1:1 ratio.	

Reporting group values	Defibrotide Prophylaxis	Standard of Care (SOC)	Total
Number of subjects	79	73	152
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 50.54 ± 16.952	 51.09 ± 16.621	 -
Gender categorical Units: Subjects			
Female	38	37	75
Male	41	36	77

End points

End points reporting groups

Reporting group title	Defibrotide Prophylaxis
Reporting group description:	
Eligible participants were randomly assigned to receive defibrotide prophylaxis.	
Reporting group title	Standard of Care (SOC)
Reporting group description:	
Eligible participants were randomly assigned to receive SoC immunoprophylaxis alone in a 1:1 ratio.	

Primary: Percentage of Participants with Cumulative Incidence of Grade B to D Acute Graft Versus Host Disease (aGvHD) by Day +100 post-Hematopoietic Stem Cell Transplant (HSCT)

End point title	Percentage of Participants with Cumulative Incidence of Grade B to D Acute Graft Versus Host Disease (aGvHD) by Day +100 post-Hematopoietic Stem Cell Transplant (HSCT)
End point description:	

End point type	Primary
End point timeframe:	
Baseline through Day +100 post-HSCT	

End point values	Defibrotide Prophylaxis	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	73		
Units: participants				
number (not applicable)	38.4	47.1		

Statistical analyses

Statistical analysis title	P-value from Stratified Gray's Test
Statistical analysis description:	
The treatment comparison on the cumulative incidence of Grade B-D aGvHD over time was conducted using a stratified Gray's test. The resulting p-value was not applicable to any specific timepoint, but rather the whole duration of the study.	
Comparison groups	Defibrotide Prophylaxis v Standard of Care (SOC)
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6656
Method	t-test, 2-sided

Secondary: Percentage of Participants with Cumulative Incidence of Grade B to D aGvHD by Day +180 post-HSCT

End point title	Percentage of Participants with Cumulative Incidence of Grade B to D aGvHD by Day +180 post-HSCT

End point description:

End point type	Secondary

End point timeframe:

Day +180 post-HSCT

End point values	Defibrotide Prophylaxis	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	73		
Units: participants				
number (not applicable)	50.6	51.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were reported from the time of signed informed consent form (ICF) and were recorded up to Day +63 post-HSCT for subjects who underwent HSCT, whereas for subjects who did not undergo HSCT, 70 days after baseline.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	defibrotide prophylaxis
Reporting group description: -	
Reporting group title	Standard of Care (SOC)

Reporting group description: -

Serious adverse events	defibrotide prophylaxis	Standard of Care (SOC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 74 (41.89%)	31 / 70 (44.29%)	
number of deaths (all causes)	10	9	
number of deaths resulting from adverse events	5	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia recurrent			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus associated lymphoproliferative disorder			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Obstructive shock			

subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
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 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Venoocclusive disease			
subjects affected / exposed	1 / 74 (1.35%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
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 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 74 (1.35%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Acute graft versus host disease			
subjects affected / exposed	4 / 74 (5.41%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute graft versus host disease in skin			
subjects affected / exposed	1 / 74 (1.35%)	4 / 70 (5.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in liver			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute graft versus host disease in intestine			
subjects affected / exposed	2 / 74 (2.70%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 74 (1.35%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 74 (4.05%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngeal inflammation			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
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	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 74 (1.35%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood potassium decreased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			

subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 74 (1.35%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stress cardiomyopathy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Evans syndrome			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (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	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombotic microangiopathy			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (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	3 / 74 (4.05%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 74 (2.70%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 74 (2.70%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Venoocclusive liver disease			
subjects affected / exposed	0 / 74 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash vesicular			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 74 (4.05%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 74 (1.35%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (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 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
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	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr viraemia			

subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (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 infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 74 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 74 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
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	2 / 74 (2.70%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (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	0 / 74 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			

subjects affected / exposed	1 / 74 (1.35%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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 prophylaxis	Standard of Care (SOC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 74 (100.00%)	70 / 70 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 74 (5.41%)	4 / 70 (5.71%)	
occurrences (all)	6	4	
Hypertension			
subjects affected / exposed	25 / 74 (33.78%)	29 / 70 (41.43%)	
occurrences (all)	40	32	
Hypotension			
subjects affected / exposed	13 / 74 (17.57%)	11 / 70 (15.71%)	
occurrences (all)	16	14	
Orthostatic hypotension			
subjects affected / exposed	6 / 74 (8.11%)	3 / 70 (4.29%)	
occurrences (all)	6	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 74 (12.16%)	6 / 70 (8.57%)	
occurrences (all)	12	6	
Catheter site pain			
subjects affected / exposed	8 / 74 (10.81%)	9 / 70 (12.86%)	
occurrences (all)	10	10	
Chills			
subjects affected / exposed	7 / 74 (9.46%)	6 / 70 (8.57%)	
occurrences (all)	8	7	
Fatigue			
subjects affected / exposed	25 / 74 (33.78%)	25 / 70 (35.71%)	
occurrences (all)	32	27	

Mucosal inflammation			
subjects affected / exposed	10 / 74 (13.51%)	17 / 70 (24.29%)	
occurrences (all)	11	24	
Oedema peripheral			
subjects affected / exposed	19 / 74 (25.68%)	21 / 70 (30.00%)	
occurrences (all)	125	24	
Pain			
subjects affected / exposed	5 / 74 (6.76%)	6 / 70 (8.57%)	
occurrences (all)	7	7	
Pyrexia			
subjects affected / exposed	28 / 74 (37.84%)	24 / 70 (34.29%)	
occurrences (all)	38	34	
Immune system disorders			
Graft versus host disease in skin			
subjects affected / exposed	4 / 74 (5.41%)	2 / 70 (2.86%)	
occurrences (all)	4	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 74 (22.97%)	16 / 70 (22.86%)	
occurrences (all)	20	20	
Dyspnoea			
subjects affected / exposed	8 / 74 (10.81%)	12 / 70 (17.14%)	
occurrences (all)	12	19	
Epistaxis			
subjects affected / exposed	12 / 74 (16.22%)	11 / 70 (15.71%)	
occurrences (all)	13	13	
Hiccups			
subjects affected / exposed	5 / 74 (6.76%)	3 / 70 (4.29%)	
occurrences (all)	5	3	
Hypoxia			
subjects affected / exposed	4 / 74 (5.41%)	3 / 70 (4.29%)	
occurrences (all)	4	7	
Nasal congestion			
subjects affected / exposed	4 / 74 (5.41%)	1 / 70 (1.43%)	
occurrences (all)	6	1	
Oropharyngeal pain			

subjects affected / exposed	9 / 74 (12.16%)	12 / 70 (17.14%)	
occurrences (all)	9	14	
Pleural effusion			
subjects affected / exposed	4 / 74 (5.41%)	3 / 70 (4.29%)	
occurrences (all)	6	4	
Productive cough			
subjects affected / exposed	5 / 74 (6.76%)	0 / 70 (0.00%)	
occurrences (all)	6	0	
Rales			
subjects affected / exposed	4 / 74 (5.41%)	2 / 70 (2.86%)	
occurrences (all)	4	4	
Rhinitis allergic			
subjects affected / exposed	2 / 74 (2.70%)	4 / 70 (5.71%)	
occurrences (all)	2	4	
Rhinorrhoea			
subjects affected / exposed	6 / 74 (8.11%)	9 / 70 (12.86%)	
occurrences (all)	7	9	
Tachypnoea			
subjects affected / exposed	4 / 74 (5.41%)	2 / 70 (2.86%)	
occurrences (all)	5	2	
Psychiatric disorders			
Agitation			
subjects affected / exposed	5 / 74 (6.76%)	3 / 70 (4.29%)	
occurrences (all)	5	3	
Anxiety			
subjects affected / exposed	11 / 74 (14.86%)	9 / 70 (12.86%)	
occurrences (all)	11	9	
Confusional state			
subjects affected / exposed	5 / 74 (6.76%)	3 / 70 (4.29%)	
occurrences (all)	6	3	
Delirium			
subjects affected / exposed	4 / 74 (5.41%)	2 / 70 (2.86%)	
occurrences (all)	5	2	
Depression			
subjects affected / exposed	7 / 74 (9.46%)	2 / 70 (2.86%)	
occurrences (all)	7	2	

Insomnia			
subjects affected / exposed	22 / 74 (29.73%)	16 / 70 (22.86%)	
occurrences (all)	24	18	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 74 (4.05%)	7 / 70 (10.00%)	
occurrences (all)	7	10	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 74 (2.70%)	5 / 70 (7.14%)	
occurrences (all)	2	6	
Bacterial test positive			
subjects affected / exposed	4 / 74 (5.41%)	3 / 70 (4.29%)	
occurrences (all)	5	6	
Blood bilirubin increased			
subjects affected / exposed	3 / 74 (4.05%)	5 / 70 (7.14%)	
occurrences (all)	5	13	
Blood creatinine increased			
subjects affected / exposed	12 / 74 (16.22%)	6 / 70 (8.57%)	
occurrences (all)	14	6	
Blood magnesium decreased			
subjects affected / exposed	1 / 74 (1.35%)	4 / 70 (5.71%)	
occurrences (all)	1	6	
C-reactive protein increased			
subjects affected / exposed	4 / 74 (5.41%)	5 / 70 (7.14%)	
occurrences (all)	4	6	
Epstein-Barr virus test positive			
subjects affected / exposed	4 / 74 (5.41%)	2 / 70 (2.86%)	
occurrences (all)	4	2	
Neutrophil count decreased			
subjects affected / exposed	8 / 74 (10.81%)	11 / 70 (15.71%)	
occurrences (all)	20	23	
Platelet count decreased			
subjects affected / exposed	19 / 74 (25.68%)	21 / 70 (30.00%)	
occurrences (all)	54	56	
Transaminases increased			

subjects affected / exposed	4 / 74 (5.41%)	6 / 70 (8.57%)	
occurrences (all)	4	7	
Weight decreased			
subjects affected / exposed	3 / 74 (4.05%)	4 / 70 (5.71%)	
occurrences (all)	4	5	
White blood cell count decreased			
subjects affected / exposed	8 / 74 (10.81%)	6 / 70 (8.57%)	
occurrences (all)	15	17	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 74 (6.76%)	2 / 70 (2.86%)	
occurrences (all)	5	2	
Infusion related reaction			
subjects affected / exposed	4 / 74 (5.41%)	6 / 70 (8.57%)	
occurrences (all)	4	6	
Limb injury			
subjects affected / exposed	4 / 74 (5.41%)	1 / 70 (1.43%)	
occurrences (all)	5	1	
Skin abrasion			
subjects affected / exposed	1 / 74 (1.35%)	4 / 70 (5.71%)	
occurrences (all)	1	5	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	9 / 74 (12.16%)	8 / 70 (11.43%)	
occurrences (all)	10	12	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 74 (13.51%)	8 / 70 (11.43%)	
occurrences (all)	11	12	
Dysgeusia			
subjects affected / exposed	10 / 74 (13.51%)	9 / 70 (12.86%)	
occurrences (all)	12	9	
Headache			
subjects affected / exposed	31 / 74 (41.89%)	23 / 70 (32.86%)	
occurrences (all)	40	36	
Restless legs syndrome			

subjects affected / exposed	5 / 74 (6.76%)	1 / 70 (1.43%)	
occurrences (all)	5	1	
Somnolence			
subjects affected / exposed	5 / 74 (6.76%)	2 / 70 (2.86%)	
occurrences (all)	7	2	
Tremor			
subjects affected / exposed	10 / 74 (13.51%)	9 / 70 (12.86%)	
occurrences (all)	11	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 74 (36.49%)	30 / 70 (42.86%)	
occurrences (all)	49	60	
Febrile neutropenia			
subjects affected / exposed	30 / 74 (40.54%)	20 / 70 (28.57%)	
occurrences (all)	32	20	
Leukopenia			
subjects affected / exposed	9 / 74 (12.16%)	6 / 70 (8.57%)	
occurrences (all)	18	12	
Neutropenia			
subjects affected / exposed	12 / 74 (16.22%)	17 / 70 (24.29%)	
occurrences (all)	28	28	
Thrombocytopenia			
subjects affected / exposed	19 / 74 (25.68%)	19 / 70 (27.14%)	
occurrences (all)	36	41	
Eye disorders			
Dry eye			
subjects affected / exposed	15 / 74 (20.27%)	6 / 70 (8.57%)	
occurrences (all)	15	7	
Eye swelling			
subjects affected / exposed	0 / 74 (0.00%)	4 / 70 (5.71%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	8 / 74 (10.81%)	5 / 70 (7.14%)	
occurrences (all)	13	6	
Abdominal pain			

subjects affected / exposed	13 / 74 (17.57%)	22 / 70 (31.43%)	
occurrences (all)	18	24	
Abdominal pain lower			
subjects affected / exposed	4 / 74 (5.41%)	0 / 70 (0.00%)	
occurrences (all)	4	0	
Abdominal pain upper			
subjects affected / exposed	5 / 74 (6.76%)	9 / 70 (12.86%)	
occurrences (all)	7	15	
Constipation			
subjects affected / exposed	28 / 74 (37.84%)	29 / 70 (41.43%)	
occurrences (all)	34	37	
Diarrhoea			
subjects affected / exposed	47 / 74 (63.51%)	53 / 70 (75.71%)	
occurrences (all)	71	77	
Dry mouth			
subjects affected / exposed	7 / 74 (9.46%)	6 / 70 (8.57%)	
occurrences (all)	8	6	
Dyspepsia			
subjects affected / exposed	4 / 74 (5.41%)	11 / 70 (15.71%)	
occurrences (all)	4	13	
Dysphagia			
subjects affected / exposed	5 / 74 (6.76%)	3 / 70 (4.29%)	
occurrences (all)	6	7	
Flatulence			
subjects affected / exposed	4 / 74 (5.41%)	3 / 70 (4.29%)	
occurrences (all)	4	3	
Haemorrhoids			
subjects affected / exposed	6 / 74 (8.11%)	6 / 70 (8.57%)	
occurrences (all)	10	6	
Mouth ulceration			
subjects affected / exposed	4 / 74 (5.41%)	1 / 70 (1.43%)	
occurrences (all)	5	1	
Nausea			
subjects affected / exposed	56 / 74 (75.68%)	49 / 70 (70.00%)	
occurrences (all)	89	70	
Odynophagia			

subjects affected / exposed	7 / 74 (9.46%)	3 / 70 (4.29%)	
occurrences (all)	9	3	
Oesophagitis			
subjects affected / exposed	5 / 74 (6.76%)	0 / 70 (0.00%)	
occurrences (all)	7	0	
Stomatitis			
subjects affected / exposed	42 / 74 (56.76%)	36 / 70 (51.43%)	
occurrences (all)	68	69	
Vomiting			
subjects affected / exposed	39 / 74 (52.70%)	38 / 70 (54.29%)	
occurrences (all)	66	62	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 74 (6.76%)	3 / 70 (4.29%)	
occurrences (all)	5	3	
Dry skin			
subjects affected / exposed	7 / 74 (9.46%)	8 / 70 (11.43%)	
occurrences (all)	7	8	
Erythema			
subjects affected / exposed	13 / 74 (17.57%)	13 / 70 (18.57%)	
occurrences (all)	18	19	
Hyperhidrosis			
subjects affected / exposed	4 / 74 (5.41%)	1 / 70 (1.43%)	
occurrences (all)	4	1	
Petechiae			
subjects affected / exposed	2 / 74 (2.70%)	4 / 70 (5.71%)	
occurrences (all)	2	4	
Pruritus			
subjects affected / exposed	11 / 74 (14.86%)	13 / 70 (18.57%)	
occurrences (all)	13	15	
Pruritus generalised			
subjects affected / exposed	4 / 74 (5.41%)	5 / 70 (7.14%)	
occurrences (all)	5	6	
Rash			
subjects affected / exposed	17 / 74 (22.97%)	19 / 70 (27.14%)	
occurrences (all)	31	27	

Rash maculo-papular			
subjects affected / exposed	7 / 74 (9.46%)	7 / 70 (10.00%)	
occurrences (all)	10	7	
Skin hyperpigmentation			
subjects affected / exposed	2 / 74 (2.70%)	5 / 70 (7.14%)	
occurrences (all)	2	5	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	17 / 74 (22.97%)	16 / 70 (22.86%)	
occurrences (all)	22	21	
Cystitis haemorrhagic			
subjects affected / exposed	2 / 74 (2.70%)	4 / 70 (5.71%)	
occurrences (all)	2	6	
Dysuria			
subjects affected / exposed	6 / 74 (8.11%)	5 / 70 (7.14%)	
occurrences (all)	7	6	
Haematuria			
subjects affected / exposed	3 / 74 (4.05%)	4 / 70 (5.71%)	
occurrences (all)	4	5	
Pollakiuria			
subjects affected / exposed	4 / 74 (5.41%)	4 / 70 (5.71%)	
occurrences (all)	6	4	
Urinary retention			
subjects affected / exposed	4 / 74 (5.41%)	0 / 70 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 74 (13.51%)	6 / 70 (8.57%)	
occurrences (all)	11	8	
Back pain			
subjects affected / exposed	8 / 74 (10.81%)	12 / 70 (17.14%)	
occurrences (all)	9	13	
Bone pain			
subjects affected / exposed	3 / 74 (4.05%)	4 / 70 (5.71%)	
occurrences (all)	4	4	
Musculoskeletal pain			

subjects affected / exposed	6 / 74 (8.11%)	1 / 70 (1.43%)	
occurrences (all)	8	1	
Myalgia			
subjects affected / exposed	6 / 74 (8.11%)	2 / 70 (2.86%)	
occurrences (all)	7	2	
Neck pain			
subjects affected / exposed	5 / 74 (6.76%)	3 / 70 (4.29%)	
occurrences (all)	6	3	
Pain in extremity			
subjects affected / exposed	5 / 74 (6.76%)	3 / 70 (4.29%)	
occurrences (all)	7	3	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	3 / 74 (4.05%)	4 / 70 (5.71%)	
occurrences (all)	3	4	
Cytomegalovirus infection			
subjects affected / exposed	11 / 74 (14.86%)	14 / 70 (20.00%)	
occurrences (all)	12	15	
Oral candidiasis			
subjects affected / exposed	0 / 74 (0.00%)	6 / 70 (8.57%)	
occurrences (all)	0	7	
Urinary tract infection			
subjects affected / exposed	3 / 74 (4.05%)	6 / 70 (8.57%)	
occurrences (all)	3	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 74 (40.54%)	30 / 70 (42.86%)	
occurrences (all)	39	37	
Dehydration			
subjects affected / exposed	4 / 74 (5.41%)	5 / 70 (7.14%)	
occurrences (all)	4	5	
Fluid overload			
subjects affected / exposed	5 / 74 (6.76%)	5 / 70 (7.14%)	
occurrences (all)	5	6	
Fluid retention			

subjects affected / exposed	6 / 74 (8.11%)	4 / 70 (5.71%)	
occurrences (all)	9	10	
Hyperglycaemia			
subjects affected / exposed	12 / 74 (16.22%)	9 / 70 (12.86%)	
occurrences (all)	24	17	
Hyperkalaemia			
subjects affected / exposed	5 / 74 (6.76%)	8 / 70 (11.43%)	
occurrences (all)	5	12	
Hypernatraemia			
subjects affected / exposed	2 / 74 (2.70%)	5 / 70 (7.14%)	
occurrences (all)	6	5	
Hypoalbuminaemia			
subjects affected / exposed	8 / 74 (10.81%)	2 / 70 (2.86%)	
occurrences (all)	9	3	
Hypocalcaemia			
subjects affected / exposed	3 / 74 (4.05%)	5 / 70 (7.14%)	
occurrences (all)	3	9	
Hypokalaemia			
subjects affected / exposed	24 / 74 (32.43%)	27 / 70 (38.57%)	
occurrences (all)	36	44	
Hypomagnesaemia			
subjects affected / exposed	30 / 74 (40.54%)	35 / 70 (50.00%)	
occurrences (all)	52	59	
Hyponatraemia			
subjects affected / exposed	8 / 74 (10.81%)	5 / 70 (7.14%)	
occurrences (all)	9	6	
Hypophagia			
subjects affected / exposed	1 / 74 (1.35%)	5 / 70 (7.14%)	
occurrences (all)	1	6	
Hypophosphataemia			
subjects affected / exposed	5 / 74 (6.76%)	11 / 70 (15.71%)	
occurrences (all)	9	25	
Malnutrition			
subjects affected / exposed	4 / 74 (5.41%)	6 / 70 (8.57%)	
occurrences (all)	4	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2018	Section 4.1 Inclusion criteria: #1 updated to remove upper limit of age <75 years for inclusion. #8 to remove requirement of negative serum pregnancy tests at Days +28 and +63 post-HSCT. Section 4.2 Exclusion criteria: #3 updated to clarify that use of heparin or other anticoagulants for routine central venous line management, and intermittent dialysis or ultrafiltration as well as fibrinolytic instillation for central venous line occlusion will be allowed. #5 updated to exclude patients receiving or planning to receive other investigational therapy #11 updated to add description on hypersensitivity to any agent in patient's planned immunoprophylaxis regimen. Added #12 on patient having any contraindications to agent(s) within immunoprophylaxis regimens allowed by protocol order to address contraindications, special precautions, and warnings for medicinal products used as standard of care (SoC). Section 5.1.2 & 5.2.2 updated to add a clarification to a reference SmPC or approved label for warnings and precautions associated with reference therapy. Section 5.2.1 to provide info on administration setting and guidance on defibrotide dosing window. Section 5.7.5 to remove prohibition against all investigational therapies. Section 6.8 to clarify that clinically significant laboratory values are to be reported as adverse events only if they are clinically significant as assessed by the investigator. Patients who do not receive HSCT, AEs will be collected up to 70 days after baseline. Section 6.8.1.7 Pregnancy has been harmonised with language in Section 6.9.1pregnancy is a reason why study drug must be permanently discontinued. Section 6.9.1 to differentiate reasons for discontinuation of a patient from the study and discontinuation from the study drug, and to differentiate between reason that 'must' and that 'may' lead to an early termination. Section 7.1 & 7.3 to clarify that bone marrow aspirate and biopsy are required for assessment of disease relapse.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported