Clinical trial results:
An Open-label, Randomized, Multi-center, Parallel Group, Two-arm Study to Assess the Safety, Overall Tolerability, and Antiviral Activity of Brincidofovir versus Standard of Care for Treatment of Adenovirus Infections in High-risk Pediatric Allogeneic Hematopoietic Cell Transplant Recipients

Summary

EudraCT number	2017-001735-39
Trial protocol	IE DE ES IT FR NL GB PL
Global end of trial date	30 May 2019

Results information

Result version number	v1 (current)
This version publication date	03 January 2020
First version publication date	03 January 2020

Trial information

Trial identification

Sponsor protocol code	CMX001-999

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Chimerix, Inc.
Sponsor organisation address	2505 Meridian Pkwy, Suite 100, Durham, United States, 27713
Public contact	Chief Medical Officer, Chimerix, Inc., +1 919 287 6006, AdAPT@chimerix.com
Scientific contact	Chief Medical Officer, Chimerix, Inc., +1 919 287 6006, AdAPT@chimerix.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001904-PIP02-17
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	30 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 May 2019
Global end of trial reached?	Yes
Global end of trial date	30 May 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the safety, overall tolerability, and virologic response of BCV vs. SoC for the treatment of AdV infection in high-risk pediatric allogeneic HCT recipients.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator:

Management of subjects randomized to the SoC treatment arm was prescribed by the investigator as being in the best interests of the subject and may have included taking a “watch-and-wait” approach, with or without decreased immunosuppression (ergo, no treatment), or treatment with other available antivirals, most commonly IV CDV. Decisions regarding SoC, including administration of therapy, dose and regimen of therapy, modification of immunosuppression, and monitoring was the responsibility of the clinical team caring for the subject, according to institutional guidelines, local practices, and applicable guidelines for the management of AdV infection. Relevant product labeling was to be followed, per the investigator’s discretion.

Actual start date of recruitment	22 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	29
EEA total number of subjects	23

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)	6
Children (2-11 years)	20
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first participant was screened on 22 December 2017. The last study visit occurred on 30 May 2019.

Pre-assignment

Screening details:

68 subjects were screened.

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	Brincidofovir

Arm description:

Subjects randomized to receive BCV were to be treated until AdV deoxyribonucleic acid (DNA) was confirmed to be undetectable in plasma, or until Week 16 post-randomization, whichever occurred first. Subjects with persistent AdV infection after 16 cumulative weeks of BCV therapy could receive treatment until a maximum cumulative treatment duration of 24 weeks.

Arm type	Experimental
Investigational medicinal product name	brincidofovir
Investigational medicinal product code	CMX001
Other name	BCV
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to the BCV treatment arm received oral BCV suspension (10 mg/mL) as follows:
For subjects NOT receiving concurrent cyclosporine on Day 1:
-If ≥ 48 kg body weight 10 mL of the 10 mg/mL oral suspension
-If < 48 kg body weight, 2 mg/kg BIW administered orally as the appropriate volume of 10 mg/mL oral suspension
For subjects receiving concurrent cyclosporine on Day 1 (or who initiate cyclosporine at any time while taking BCV):
-1.4 mg/kg (up to a maximum of 70 mg) BIW administered orally as the appropriate volume of 10 mg/mL oral suspension

Arm title	Standard of Care

Arm description:

Subjects randomized to the SoC arm were to be managed according to local or institutional practice guidelines for the treatment of AdV infection, which may have included other drugs or using a watch and wait approach.

Arm type	Standard of Care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Brincidofovir	Standard of Care
Started	20	9
Completed	11	5
Not completed	9	4
Consent withdrawn by subject	2	-
Death	2	1
Not given	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Brincidofovir
Reporting group description:	
Subjects randomized to receive BCV were to be treated until AdV deoxyribonucleic acid (DNA) was confirmed to be undetectable in plasma, or until Week 16 post-randomization, whichever occurred first. Subjects with persistent AdV infection after 16 cumulative weeks of BCV therapy could receive treatment until a maximum cumulative treatment duration of 24 weeks.	
Reporting group title	Standard of Care
Reporting group description:	
Subjects randomized to the SoC arm were to be managed according to local or institutional practice guidelines for the treatment of AdV infection, which may have included other drugs or using a watch and wait approach.	

Reporting group values	Brincidofovir	Standard of Care	Total
Number of subjects	20	9	29
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	4	2	6
Children (2-11 years)	14	6	20
Adolescents (12-17 years)	2	1	3
Gender categorical Units: Subjects			
Female	8	5	13
Male	12	4	16

End points

End points reporting groups

Reporting group title	Brincidofovir

Reporting group description:

Subjects randomized to receive BCV were to be treated until AdV deoxyribonucleic acid (DNA) was confirmed to be undetectable in plasma, or until Week 16 post-randomization, whichever occurred first. Subjects with persistent AdV infection after 16 cumulative weeks of BCV therapy could receive treatment until a maximum cumulative treatment duration of 24 weeks.

Reporting group title	Standard of Care

Reporting group description:

Subjects randomized to the SoC arm were to be managed according to local or institutional practice guidelines for the treatment of AdV infection, which may have included other drugs or using a watch and wait approach.

Primary: Time-averaged area under the concentration-time curve (AAUC) for AdV viremia

End point title	Time-averaged area under the concentration-time curve (AAUC) for AdV viremia[1]

End point description:

The primary AAUC analysis was to utilize all randomized subjects (ITT) in an analysis of covariance (ANCOVA) from randomization through Week 16 post-randomization with all stratification factors included in the model: T cell-depletion method (alemtuzumab or ex vivo cell selection vs. ATG), time from HCT to randomization (< 28 days vs. ≥ 28 days), and baseline AdV viremia (continuous log10 copies/mL).

End point type	Primary

End point timeframe:

16 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was terminated early due to poor subject accrual rates. The small number of subjects enrolled (29) was not adequate to conduct the planned analyses.

End point values	Brincidofovir	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: log10 copies/mL				

Notes:

[2] - The study was terminated early due to poor subject accrual rates and analyses not performed.

[3] - The study was terminated early due to poor subject accrual rates and analyses not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of all-cause mortality through Week 16

End point title	Incidence of all-cause mortality through Week 16

End point description:

Incidence of all-cause mortality through Week 16

End point type	Secondary

End point timeframe:
16 weeks

End point values	Brincidofovir	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Percentage				

Notes:
[4] - Study terminate early
[5] - Study terminated early

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs through Week 16 were to be recorded; after Week 16, if the subject reinitiated BCV therapy all AEs were to be recorded as long as the subject remained on BCV and until 4 weeks after the last dose of BCV or completion of the Week 36 assessment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Brincidofovir

Reporting group description:

Subjects randomized to receive BCV were to be treated until AdV deoxyribonucleic acid (DNA) was confirmed to be undetectable in plasma, or until Week 16 post-randomization, whichever occurred first. Subjects with persistent AdV infection after 16 cumulative weeks of BCV therapy could receive treatment until a maximum cumulative treatment duration of 24 weeks.

Reporting group title	Standard of Care

Reporting group description:

Subjects randomized to the SoC arm were to be managed according to local or institutional practice guidelines for the treatment of AdV infection, which may have included other drugs or using a watch and wait approach.

Serious adverse events	Brincidofovir	Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 20 (75.00%)	6 / 9 (66.67%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	3 / 9 (33.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unevaluable event			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Astrovirus test positive			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine abnormal			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (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 / 20 (5.00%)	0 / 9 (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			
Encephalopathy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (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			
Evans syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (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 distension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (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 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Venoocclusive liver disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (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	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human herpesvirus 6 infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

fungal			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (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	Brincidofovir	Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)	9 / 9 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 20 (10.00%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Catheter site inflammation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	7 / 20 (35.00%)	2 / 9 (22.22%)	
occurrences (all)	7	2	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Drug hypersensitivity			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Engraftment syndrome			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Graft versus host disease			
subjects affected / exposed	0 / 20 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Graft versus host disease in skin			
subjects affected / exposed	2 / 20 (10.00%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Nasal congestion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pneumomediastinum			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Sinus congestion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 20 (10.00%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Amylase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Blood albumin			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	2 / 20 (10.00%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Blood creatinine increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Blood magnesium decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Blood potassium			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood uric acid increased			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Clostridium test			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Fluid balance positive			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 20 (20.00%)	2 / 9 (22.22%)	
occurrences (all)	4	2	
Haemoglobin decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Liver function test increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Viral test positive			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Bite			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Spinal compression fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Lethargy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Febrile neutropenia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	

Haemolytic uraemic syndrome			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Lymphadenectomy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	2 / 20 (10.00%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Thrombocytopenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Thrombotic microangiopathy			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Retinal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 20 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	5	1	
Abdominal pain upper			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Anal fissure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Constipation			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	7 / 20 (35.00%)	0 / 9 (0.00%)	
occurrences (all)	7	0	
Dyspepsia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastric haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Ileus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lip dry			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	4 / 20 (20.00%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Pneumatosis intestinalis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	5 / 20 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	5	1	
Pneumoperitoneum			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Venoocclusive liver disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dermatitis diaper			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	2 / 20 (10.00%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Eczema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 20 (5.00%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Rash erythematous			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash generalised			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Skin irritation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
BK virus infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Bronchiolitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Encephalitis			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Epstein-Barr viraemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Epstein-Barr virus infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Escherichia infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pseudomonas infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Purulent discharge			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Staphylococcal skin infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Streptococcal bacteraemia			

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 20 (15.00%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Fluid overload			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Hypomagnesaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hypophosphataemia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 9 (11.11%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2017	•Allowed treatment with BCV after Week 16 in either treatment group up to a maximum cumulative duration of 24 weeks. •If the first AdV viremia result from the designated central virology laboratory was reported at ≥ 10,000 copies a confirmatory sample was not required
06 August 2018	•Revised to include allogeneic HCT recipients of a T cell-depleted and/or unrelated cord blood graft •Revised the inclusion criteria to limit enrollment in patients who had received no more than 10 mg/kg cumulative exposure to IV cidofovir within 21-day window prior to randomization •Added a new secondary efficacy endpoint assessing the clearance of AdV from stool (and other non-blood matrices) •The acceptability/palatability of the BCV oral suspension formulation was to be evaluated at selected study centers
01 February 2019	•Inclusion criteria revised to include pediatric allogeneic hematopoietic cell transplant recipients of a T cell-replete graft from a haploidentical donor when also treated with high-dose cyclophosphamide for graft versus host disease prophylaxis •Revised to allow cross-over between BCV and SoC arms

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 May 2019	Study terminated early	-

Notes:

Limitations and caveats

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

The study was terminated early due to poor subject accrual rates and not for safety reasons. The small number of subjects enrolled (29) was not adequate to conduct the planned analyses.

Notes: