Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study of the Safety, Tolerability, and Efficacy of CMX001 for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R+) Hematopoietic Stem Cell Transplant Recipients

Summary

EudraCT number	2013-004795-35
Trial protocol	BE
Global end of trial date	15 January 2016

Results information

Result version number	v1 (current)
This version publication date	24 September 2021
First version publication date	24 September 2021

Trial information

Trial identification

Sponsor protocol code	CMX001-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01769170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chimerix, Inc.
Sponsor organisation address	2505 Meridian Parkway Suite 100, Durham, NC, United States, 27713
Public contact	Main Phone Number, Chimerix, Inc., 1 919 806 1074, clinicaltrials@chimerix.com
Scientific contact	Main Phone Number, Chimerix, Inc., 1 919 806 1074, clinicaltrials@chimerix.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2015
Global end of trial reached?	Yes
Global end of trial date	15 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of brincidofovir to placebo for the prevention of clinically significant CMV infection in R+ allogeneic hematopoietic stem cell transplant (HSCT) recipients. Additionally the trial was designed to compare the safety and tolerability of brincidofovir to placebo for the prevention of clinically significant CMV infection in R+ allogeneic HSCT recipients

Protection of trial subjects:

During the treatment phase of the study, treatment-emergent AEs (TEAEs) were managed according to the Safety Monitoring and Management Plan (SMMP) developed for the BCV clinical program. The SMMP allowed for sequential dose interruption, change in dose frequency from twice- to once weekly with the same total weekly dose ("dose modification"), and a one-half reduction in the once weekly dose ("dose reduction"), as necessary. The study blind was maintained during these dosing changes.

Independent safety oversight was provided by a Data and Safety Monitoring Board (DSMB), which was convened according to Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines on clinical study data monitoring committees. The DSMB monitored safety for this study, reviewing unblinded safety data on an ongoing basis on a schedule determined by the DSMB and detailed in the DSMB charter.

Background therapy:

None.

Evidence for comparator:

Placebo was used as the comparator. Subjects randomized to the placebo treatment arm received one matched placebo tablet, administered orally, twice-weekly. Each placebo dose was administered under the same conditions as the test product.

Actual start date of recruitment	02 September 2013
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	Canada: 7
Country: Number of subjects enrolled	United States: 439
Country: Number of subjects enrolled	Belgium: 6
Worldwide total number of subjects	452
EEA total number of subjects	6

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	339
From 65 to 84 years	113
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 44 study centers located in the USA (39 centers), Canada (3 centers), and Belgium (2 centers). The first subject was screened on 22 August 2013 and the last subject completed on 12 November 2015.

Pre-assignment

Screening details:

A total of 568 HCT patients were screened for participation in this study and 458 subjects were randomized to study treatment. Of the 110 patients assessed as screen failures, almost three-quarters (79 of 110, 72%) were excluded from the study due to a positive CMV viremia result.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

Blinding was maintained by the use of placebo tablets matched to brincidofovir tablets.

Arms

Are arms mutually exclusive?	Yes
Arm title	Brincidofovir Group

Arm description:

Subjects randomized to the active treatment arm received 100 mg brincidofovir, administered orally, as one 100 mg tablet twice-weekly (i.e., at alternating 3- and 4-day intervals). All brincidofovir doses were to be given with or within 30 minutes after finishing a low-fat meal.

Arm type	Experimental
Investigational medicinal product name	brincidofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to the active treatment arm received 100 mg BCV, administered orally, as one 100 mg tablet twice-weekly (i.e., at alternating 3- and 4-day intervals) for up to 14 weeks.

Arm title	Placebo Group

Arm description:

Subjects randomized to the placebo treatment arm received one matched placebo tablet, administered orally, twice-weekly. Each placebo dose was administered under the same conditions described above for the test product.

Arm type	Placebo
Investigational medicinal product name	brincidofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to the active treatment arm received 100 mg BCV, administered orally, as one 100 mg tablet twice-weekly (i.e., at alternating 3- and 4-day intervals) for up to 14 weeks.

Number of subjects in period 1	Brincidofovir Group	Placebo Group
Started	303	149
Completed	116	69
Not completed	187	80
Adverse event, serious fatal	12	1
Physician decision	9	4
Consent withdrawn by subject	28	9
Study drug compliance	2	-
No reason specified	7	-
Disease progression	-	1
Preemptive therapy	45	51
Adverse event, non-fatal	77	11
Qualifying disease progression	4	-
Not specified	-	2
Prohibited medication	1	1
CMV disease	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Brincidofovir Group
Reporting group description:	
Subjects randomized to the active treatment arm received 100 mg brincidofovir, administered orally, as one 100 mg tablet twice-weekly (i.e., at alternating 3- and 4-day intervals). All brincidofovir doses were to be given with or within 30 minutes after finishing a low-fat meal.	
Reporting group title	Placebo Group
Reporting group description:	
Subjects randomized to the placebo treatment arm received one matched placebo tablet, administered orally, twice-weekly. Each placebo dose was administered under the same conditions described above for the test product.	

Reporting group values	Brincidofovir Group	Placebo Group	Total
Number of subjects	303	149	452
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	230	109	339
From 65-84 years	73	40	113
85 years and over	0	0	0
< 65 years	0	0	0
>/= 65 years	0	0	0
Age continuous Units: years			
median	56	54	
full range (min-max)	18 to 77	20 to 75	-
Gender categorical Units: Subjects			
Female	140	51	191
Male	163	98	261

Subject analysis sets	
Subject analysis set title	Intent-to-Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomized to brincidofovir or placebo who received at least one dose of study drug.	

Reporting group values	Intent-to-Treat Population		
Number of subjects	452		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	230		
From 65-84 years	73		
85 years and over	0		
< 65 years	0		
>/= 65 years	0		
Age continuous Units: years			
median	56		
full range (min-max)	18 to 77		
Gender categorical Units: Subjects			
Female	191		
Male	261		

End points

End points reporting groups

Reporting group title	Brincidofovir Group

Reporting group description:

Subjects randomized to the active treatment arm received 100 mg brincidofovir, administered orally, as one 100 mg tablet twice-weekly (i.e., at alternating 3- and 4-day intervals). All brincidofovir doses were to be given with or within 30 minutes after finishing a low-fat meal.

Reporting group title	Placebo Group

Reporting group description:

Subjects randomized to the placebo treatment arm received one matched placebo tablet, administered orally, twice-weekly. Each placebo dose was administered under the same conditions described above for the test product.

Subject analysis set title	Intent-to-Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to brincidofovir or placebo who received at least one dose of study drug.

Primary: Incidence of Clinically Significant CMV Infection Through Week 24

End point title	Incidence of Clinically Significant CMV Infection Through Week 24

End point description:

The primary efficacy endpoint of this study was the incidence of clinically significant CMV infection through Week 24 (i.e., Day 168 post-transplant ± 14 days), where "clinically significant CMV infection" was defined by either of the following outcomes: (1) onset of CMV end-organ disease, or (2) initiation of anti CMV-specific PrT based on documented CMV viremia (as measured by the central virology laboratory) and the clinical condition of the subject.

End point type	Primary

End point timeframe:

24 Weeks

End point values	Brincidofovir Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	149		
Units: Subjects with CMV Infection				
Subjects with clinically significant CMV	155	78		
Subjects without clinically significant CMV	148	71		

Statistical analyses

Statistical analysis title	CHM test
Comparison groups	Brincidofovir Group v Placebo Group

Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.805
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.41

Secondary: Incidence of Clinically Significant CMV Infection Through Week 14

End point title	Incidence of Clinically Significant CMV Infection Through Week 14

End point description:

The incidence of clinically significant cytomegalovirus (CMV) infection through Week 14. Blood and urine for virologic evaluations were collected at screening, pre-dose on the first day of study drug administration, and at pre-specified intervals throughout the treatment phases of the study and sent to a designated central virology laboratory for analysis. Blood samples were used for real-time assay of CMV viremia in plasma using a qPCR assay. Urine samples were stored for possible future retrospective analyses of CMV.

End point type	Secondary

End point timeframe:

14 weeks

End point values	Brincidofovir Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	149		
Units: Subjects				
Subjects with clinically significant CMV	74	57		
Subjects without clinically significant CMV	229	92		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were defined as events that began on or after the date of the first dose of study drug and on or before 7 days after the date of the last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Brincidofovir

Reporting group description:

Subjects randomized to the active treatment arm received 100 mg brincidofovir, administered orally, as one 100 mg tablet twice-weekly (i.e., at alternating 3- and 4-day intervals). All brincidofovir doses were to be given with or within 30 minutes after finishing a low-fat meal.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to the placebo treatment arm received one matched placebo tablet, administered orally, twice-weekly. Each placebo dose was administered under the same conditions described above for the test product.

Serious adverse events	Brincidofovir	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	173 / 303 (57.10%)	56 / 149 (37.58%)	
number of deaths (all causes)	47	15	
number of deaths resulting from adverse events	29	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	6 / 303 (1.98%)	3 / 149 (2.01%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 5	0 / 3	
Burkitt's lymphoma recurrent			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukaemia recurrent			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lymphoma			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Plasma cell leukaemia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 303 (0.99%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypotension			
subjects affected / exposed	3 / 303 (0.99%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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			
Chest pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multi-organ failure			
subjects affected / exposed	4 / 303 (1.32%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	9 / 303 (2.97%)	8 / 149 (5.37%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	98 / 303 (32.34%)	9 / 149 (6.04%)	
occurrences causally related to treatment / all	0 / 98	0 / 9	
deaths causally related to treatment / all	0 / 14	0 / 0	
Chronic graft versus host disease			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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			
Diffuse alveolar damage			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	3 / 303 (0.99%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 303 (0.66%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
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 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	4 / 303 (1.32%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
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	6 / 303 (1.98%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 303 (1.32%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial test positive			
subjects affected / exposed	0 / 303 (0.00%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Citrobacter test positive			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Enterococcus test positive			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia test positive			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human rhinovirus test positive			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	2 / 303 (0.66%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyomavirus test positive			
subjects affected / exposed	2 / 303 (0.66%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas test positive			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus test positive			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			

subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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			
Clavicle fracture			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed engraftment			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	4 / 303 (1.32%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
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	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			

subjects affected / exposed	2 / 303 (0.66%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ulna fracture			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	4 / 303 (1.32%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			

subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulseless electrical activity			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	3 / 303 (0.99%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	3 / 303 (0.99%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			

subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 303 (0.66%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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			
Anaemia			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 303 (1.98%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 303 (1.65%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic pseudo-obstruction			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	21 / 303 (6.93%)	4 / 149 (2.68%)	
occurrences causally related to treatment / all	14 / 21	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	5 / 303 (1.65%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
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 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	3 / 303 (0.99%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			

subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
subjects affected / exposed	2 / 303 (0.66%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	9 / 303 (2.97%)	4 / 149 (2.68%)	
occurrences causally related to treatment / all	1 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 303 (0.66%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	2 / 303 (0.66%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	9 / 303 (2.97%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	5 / 303 (1.65%)	4 / 149 (2.68%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 303 (0.99%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BK virus infection			
subjects affected / exposed	2 / 303 (0.66%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	2 / 303 (0.66%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	2 / 303 (0.66%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterovirus infection			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 303 (0.66%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 303 (0.00%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis klebsiella			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			

subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
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 / 303 (0.00%)	1 / 149 (0.67%)	
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 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocardiosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			

subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxoplasmosis			

subjects affected / exposed	2 / 303 (0.66%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral haemorrhagic cystitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Zygomycosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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			
Decreased appetite			
subjects affected / exposed	5 / 303 (1.65%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 303 (0.99%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			

subjects affected / exposed	0 / 303 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 303 (0.33%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 303 (0.33%)	0 / 149 (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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	302 / 303 (99.67%)	146 / 149 (97.99%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	33 / 303 (10.89%)	16 / 149 (10.74%)	
occurrences (all)	33	16	
Hypotension			

subjects affected / exposed	32 / 303 (10.56%)	6 / 149 (4.03%)	
occurrences (all)	32	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	42 / 303 (13.86%)	28 / 149 (18.79%)	
occurrences (all)	42	28	
Oedema peripheral			
subjects affected / exposed	52 / 303 (17.16%)	18 / 149 (12.08%)	
occurrences (all)	52	18	
Pyrexia			
subjects affected / exposed	42 / 303 (13.86%)	27 / 149 (18.12%)	
occurrences (all)	42	27	
Asthenia			
subjects affected / exposed	29 / 303 (9.57%)	6 / 149 (4.03%)	
occurrences (all)	29	6	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	173 / 303 (57.10%)	48 / 149 (32.21%)	
occurrences (all)	173	48	
Hypogammaglobulinaemia			
subjects affected / exposed	16 / 303 (5.28%)	6 / 149 (4.03%)	
occurrences (all)	16	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 303 (10.23%)	20 / 149 (13.42%)	
occurrences (all)	31	20	
Oropharyngeal pain			
subjects affected / exposed	20 / 303 (6.60%)	7 / 149 (4.70%)	
occurrences (all)	20	7	
Dyspnoea			
subjects affected / exposed	16 / 303 (5.28%)	8 / 149 (5.37%)	
occurrences (all)	16	8	
Epistaxis			
subjects affected / exposed	15 / 303 (4.95%)	9 / 149 (6.04%)	
occurrences (all)	15	9	
Rhinorrhoea			

subjects affected / exposed	10 / 303 (3.30%)	8 / 149 (5.37%)	
occurrences (all)	10	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	31 / 303 (10.23%)	12 / 149 (8.05%)	
occurrences (all)	31	12	
Depression			
subjects affected / exposed	20 / 303 (6.60%)	6 / 149 (4.03%)	
occurrences (all)	20	6	
Anxiety			
subjects affected / exposed	14 / 303 (4.62%)	10 / 149 (6.71%)	
occurrences (all)	14	10	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	34 / 303 (11.22%)	9 / 149 (6.04%)	
occurrences (all)	34	9	
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 303 (6.60%)	8 / 149 (5.37%)	
occurrences (all)	20	8	
Blood creatine increased			
subjects affected / exposed	24 / 303 (7.92%)	12 / 149 (8.05%)	
occurrences (all)	24	12	
Weight decreased			
subjects affected / exposed	24 / 303 (7.92%)	2 / 149 (1.34%)	
occurrences (all)	24	2	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	18 / 303 (5.94%)	4 / 149 (2.68%)	
occurrences (all)	18	4	
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 303 (10.23%)	21 / 149 (14.09%)	
occurrences (all)	31	21	
Dizziness			
subjects affected / exposed	22 / 303 (7.26%)	13 / 149 (8.72%)	
occurrences (all)	22	13	

Tremor			
subjects affected / exposed	20 / 303 (6.60%)	10 / 149 (6.71%)	
occurrences (all)	20	10	
Dysgeusia			
subjects affected / exposed	18 / 303 (5.94%)	9 / 149 (6.04%)	
occurrences (all)	18	9	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	19 / 303 (6.27%)	11 / 149 (7.38%)	
occurrences (all)	19	11	
Anaemia			
subjects affected / exposed	18 / 303 (5.94%)	7 / 149 (4.70%)	
occurrences (all)	18	7	
Neutropenia			
subjects affected / exposed	16 / 303 (5.28%)	8 / 149 (5.37%)	
occurrences (all)	16	8	
Thrombocytopenia			
subjects affected / exposed	16 / 303 (5.28%)	3 / 149 (2.01%)	
occurrences (all)	16	3	
Eye disorders			
Dry eye			
subjects affected / exposed	15 / 303 (4.95%)	11 / 149 (7.38%)	
occurrences (all)	15	11	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	184 / 303 (60.73%)	54 / 149 (36.24%)	
occurrences (all)	184	54	
Abdominal pain			
subjects affected / exposed	104 / 303 (34.32%)	26 / 149 (17.45%)	
occurrences (all)	104	26	
Nausea			
subjects affected / exposed	93 / 303 (30.69%)	29 / 149 (19.46%)	
occurrences (all)	93	29	
Vomiting			
subjects affected / exposed	74 / 303 (24.42%)	25 / 149 (16.78%)	
occurrences (all)	74	25	
Constipation			

subjects affected / exposed	29 / 303 (9.57%)	11 / 149 (7.38%)	
occurrences (all)	29	11	
Dry mouth			
subjects affected / exposed	21 / 303 (6.93%)	13 / 149 (8.72%)	
occurrences (all)	21	13	
Abdominal distension			
subjects affected / exposed	19 / 303 (6.27%)	10 / 149 (6.71%)	
occurrences (all)	19	10	
Dyspepsia			
subjects affected / exposed	24 / 303 (7.92%)	4 / 149 (2.68%)	
occurrences (all)	24	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	43 / 303 (14.19%)	28 / 149 (18.79%)	
occurrences (all)	43	28	
Pruritus			
subjects affected / exposed	29 / 303 (9.57%)	13 / 149 (8.72%)	
occurrences (all)	29	13	
Dry skin			
subjects affected / exposed	27 / 303 (8.91%)	8 / 149 (5.37%)	
occurrences (all)	27	8	
Erythema			
subjects affected / exposed	16 / 303 (5.28%)	4 / 149 (2.68%)	
occurrences (all)	16	4	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	30 / 303 (9.90%)	10 / 149 (6.71%)	
occurrences (all)	30	10	
Pollakiuria			
subjects affected / exposed	20 / 303 (6.60%)	10 / 149 (6.71%)	
occurrences (all)	20	10	
Dysuria			
subjects affected / exposed	17 / 303 (5.61%)	10 / 149 (6.71%)	
occurrences (all)	17	10	
Musculoskeletal and connective tissue disorders			

Pain in extremity			
subjects affected / exposed	26 / 303 (8.58%)	8 / 149 (5.37%)	
occurrences (all)	26	8	
Back pain			
subjects affected / exposed	22 / 303 (7.26%)	10 / 149 (6.71%)	
occurrences (all)	22	10	
Arthralgia			
subjects affected / exposed	13 / 303 (4.29%)	12 / 149 (8.05%)	
occurrences (all)	13	12	
Myalgia			
subjects affected / exposed	9 / 303 (2.97%)	8 / 149 (5.37%)	
occurrences (all)	9	8	
Infections and infestations			
BK virus infection			
subjects affected / exposed	24 / 303 (7.92%)	7 / 149 (4.70%)	
occurrences (all)	24	7	
Clostridium difficile colitis			
subjects affected / exposed	27 / 303 (8.91%)	3 / 149 (2.01%)	
occurrences (all)	27	3	
Cystitis viral			
subjects affected / exposed	17 / 303 (5.61%)	4 / 149 (2.68%)	
occurrences (all)	17	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	67 / 303 (22.11%)	19 / 149 (12.75%)	
occurrences (all)	67	19	
Hyperglycaemia			
subjects affected / exposed	48 / 303 (15.84%)	11 / 149 (7.38%)	
occurrences (all)	48	11	
Hypokalaemia			
subjects affected / exposed	47 / 303 (15.51%)	10 / 149 (6.71%)	
occurrences (all)	47	10	
Hypomagnesaemia			
subjects affected / exposed	38 / 303 (12.54%)	12 / 149 (8.05%)	
occurrences (all)	38	12	
Mucosal inflammation			

subjects affected / exposed	32 / 303 (10.56%)	15 / 149 (10.07%)	
occurrences (all)	32	15	
Hyponatraemia			
subjects affected / exposed	21 / 303 (6.93%)	8 / 149 (5.37%)	
occurrences (all)	21	8	
Hyperkalaemia			
subjects affected / exposed	20 / 303 (6.60%)	6 / 149 (4.03%)	
occurrences (all)	20	6	
Hypoalbuminaemia			
subjects affected / exposed	21 / 303 (6.93%)	5 / 149 (3.36%)	
occurrences (all)	21	5	
Dehydration			
subjects affected / exposed	20 / 303 (6.60%)	5 / 149 (3.36%)	
occurrences (all)	20	5	
Hypocalcaemia			
subjects affected / exposed	19 / 303 (6.27%)	4 / 149 (2.68%)	
occurrences (all)	19	4	
Hypophosphataemia			
subjects affected / exposed	17 / 303 (5.61%)	4 / 149 (2.68%)	
occurrences (all)	17	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	Add a new study objective and corresponding secondary endpoint to compare reconstitution of the anti-CMV immunological response between BCV-treated subjects and placebo recipients. The definition of "high-dose steroid therapy" used throughout the protocol was revised to ≥ 1 mg/kg prednisone equivalent. Inclusion criterion 1 was revised to reflect the updated definition of a CMV viremia negative result. Guidance provided for toxicity management was revised. Expanded number of participant countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported