Clinical trial results:
A Phase III Randomized, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipient

Summary

EudraCT number	2013-003831-31
Trial protocol	SE LT IT FI AT ES BE PL GB
Global end of trial date	21 November 2016

Results information

Result version number	v2 (current)
This version publication date	02 December 2017
First version publication date	19 October 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	8228-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02137772
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	21 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study evaluated the efficacy and safety of letermovir (MK-8228) for the prevention of clinically-significant CMV infection in adult, CMV-seropositive recipients of allogeneic hematopoietic stem cell transplant (HSCT). The hypothesis being tested was that MK-8228 is superior to placebo in the prevention of clinically-significant CMV infection through Week 24 post-transplant.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2014
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	Austria: 28
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	Japan: 36
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Turkey: 36
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 203

Country: Number of subjects enrolled	Sweden: 20
Worldwide total number of subjects	570
EEA total number of subjects	249

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)	482
From 65 to 84 years	88
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants had documented seropositivity for CMV within 1 year before transplant. A total of 738 participants were screened, 570 were randomized 2:1 letermovir:placebo, and 565 received at least one dose of study medication.

Pre-assignment

Screening details:

Screening could occur up to 15 days before transplant and no more than 28 days post-transplant. From the time of screening to randomization, participants were tested weekly for CMV viremia; a positive test resulted in exclusion from the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Letermovir

Arm description:

Letermovir oral or intravenous (IV) formulation was administered once daily for up to 14 weeks, beginning up to Day 28 post-transplant. The dose was 240 mg once daily for participants receiving concomitant cyclosporin A and 480 mg once daily for participants not receiving cyclosporin A. Intravenous infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets.

Arm type	Experimental
Investigational medicinal product name	Letermovir Intravenous
Investigational medicinal product code	
Other name	MK-8228
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Letermovir 240 mg once daily for up to 14 weeks beginning up to Day 28 post-transplant for participants receiving concomitant cyclosporin A and 480 mg once daily for 14 weeks beginning up to Day 28 post-transplant for participants not receiving cyclosporine A. IV infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets. Infusion was administered in 250 mL over 60 minutes.

Investigational medicinal product name	Letermovir Oral
Investigational medicinal product code	
Other name	MK-8228
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letermovir 240 mg once daily for up to 14 weeks beginning up to Day 28 post-transplant for participants receiving concomitant cyclosporin A and 480 mg once daily for 14 weeks beginning up to Day 28 post-transplant for participants not receiving cyclosporin A.

Arm title	Placebo

Arm description:

Placebo oral or IV formulation was administered once daily for up to 14 weeks, beginning up to Day 28 post-transplant. The number of placebo tablets was to mimic that for letermovir administration according to the concomitant cyclosporin A status. Intravenous infusion was administered only to

participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets.

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

Dosage and administration details:

Placebo once daily for up to 14 weeks beginning up to Day 28 post-transplant. IV infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets. Infusion was administered in 250 mL over 60 minutes.

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

Dosage and administration details:

Placebo once daily for up to 14 weeks beginning up to Day 28 post-transplant. The number of placebo tablets was to mimic that for letermovir administration according to the concomitant cyclosporin A status.

Number of subjects in period 1	Letermovir	Placebo
Started	376	194
Treated participants	373	192
Completed	244	119
Not completed	132	75
Adverse event, serious fatal	71	44
Physician decision	15	5
Consent withdrawn by subject	28	17
Adverse event, non-fatal	6	3
Non-compliance with study drug	1	-
Lost to follow-up	8	4
Not treated	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Letermovir
Reporting group description:	
Letermovir oral or intravenous (IV) formulation was administered once daily for up to 14 weeks, beginning up to Day 28 post-transplant. The dose was 240 mg once daily for participants receiving concomitant cyclosporin A and 480 mg once daily for participants not receiving cyclosporin A. Intravenous infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets.	
Reporting group title	Placebo
Reporting group description:	
Placebo oral or IV formulation was administered once daily for up to 14 weeks, beginning up to Day 28 post-transplant. The number of placebo tablets was to mimic that for letermovir administration according to the concomitant cyclosporin A status. Intravenous infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets.	

Reporting group values	Letermovir	Placebo	Total
Number of subjects	376	194	570
Age categorical Units: Subjects			
Adults (18-64 years)	320	162	482
From 65-84 years	56	32	88
Age Continuous Units: Years			
arithmetic mean	50.8	50.8	
standard deviation	± 13.4	± 14.8	-
Gender, Male/Female Units: Subjects			
Female	162	77	239
Male	214	117	331
Risk Stratum for CMV Reactivation			
High risk: Participants meeting one or more of the following criteria at randomization: 1) Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at an HLA-A, -B or -DR gene loci 2) Haploidentical donor, 3) Unrelated donor with at least one mismatch at HLA- HLA-A, -B, -C or -DRB1 gene loci 4) Use of umbilical cord blood as stem cell source, 5) Use of ex vivo T-cell-depleted grafts, 6) Grade 2 or greater graft-versus-host disease requiring the use of systemic corticosteroids. Low risk: All other participants			
Units: Subjects			
High risk	122	54	176
Low risk	254	140	394

End points

End points reporting groups

Reporting group title	Letermovir

Reporting group description:

Letermovir oral or intravenous (IV) formulation was administered once daily for up to 14 weeks, beginning up to Day 28 post-transplant. The dose was 240 mg once daily for participants receiving concomitant cyclosporin A and 480 mg once daily for participants not receiving cyclosporin A. Intravenous infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets.

Reporting group title	Placebo

Reporting group description:

Placebo oral or IV formulation was administered once daily for up to 14 weeks, beginning up to Day 28 post-transplant. The number of placebo tablets was to mimic that for letermovir administration according to the concomitant cyclosporin A status. Intravenous infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets.

Primary: Percentage of Participants with Clinically-significant CMV Infection up to Week 24 Post-transplant

End point title	Percentage of Participants with Clinically-significant CMV Infection up to Week 24 Post-transplant

End point description:

Clinically-significant CMV infection was defined as either one of the following: 1) onset of CMV end-organ disease, or 2) initiation of anti-CMV pre-emptive therapy based on documented CMV viremia and the clinical condition of the participant. The percentage of participants with clinically-significant CMV infection was assessed. The Full Analysis Set (FAS) was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated. Participants who prematurely discontinued from the study or had a missing outcome through the 24-week visit window were considered treatment failure (i.e. Non-completers equal failure [NC=F] approach was used).

End point type	Primary

End point timeframe:

Up to Week 24 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	170		
Units: Percentage of participants				
number (not applicable)	37.5	60.6		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The Mantel Haenszel analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation)

Comparison groups	Letermovir v Placebo

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-23.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.5
upper limit	-14.6

Notes:

[1] - A 1-sided p-value ≤0.0249 for the risk difference was used for declaring statistical significance

Secondary: Time to Onset of Clinically-significant CMV Infection (Kaplan-Meier Estimate of Percentage of Participants with a Qualifying Event at Week 24 Post-transplant)

End point title	Time to Onset of Clinically-significant CMV Infection (Kaplan-Meier Estimate of Percentage of Participants with a Qualifying Event at Week 24 Post-transplant)

End point description:

Clinically-significant CMV infection was defined as either one of the following: 1) onset of CMV end-organ disease, or 2) initiation of anti-CMV pre-emptive therapy based on documented CMV viremia and the clinical condition of the participant. Time to onset of clinically-significant CMV infection was defined from the day of transplantation to the day the participant developed clinically-significant CMV infection, and was analyzed by the Kaplan-Meier method. Participants were censored at the last assessment for participants who discontinued or did not develop clinically-significant CMV infection. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated.

End point type	Secondary

End point timeframe:

Up to Week 24 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	170		
Units: Percentage of participants				
number (confidence interval 95%)	18.9 (14.4 to 23.5)	44.3 (36.4 to 52.1)		

Statistical analyses

Statistical analysis title	Log Rank

Statistical analysis description:

The log rank test was adjusted for sample size for each stratum (high or low risk for CMV reactivation)

Comparison groups	Letermovir v Placebo

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [2]
Method	Logrank

Notes:

[2] - Nominal 2-sided p-value

Secondary: Percentage of Participants with Clinically-significant CMV Infection up to Week 14 Post-transplant

End point title	Percentage of Participants with Clinically-significant CMV Infection up to Week 14 Post-transplant

End point description:

Clinically-significant CMV infection was defined as either one of the following: 1) onset of CMV end-organ disease, or 2) initiation of anti-CMV pre-emptive therapy based on documented CMV viremia and the clinical condition of the participant. The percentage of participants with clinically-significant CMV infection was assessed. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated. Participants who prematurely discontinued from the study or had a missing outcome through the 14-week visit window were considered treatment failure (i.e. NC=F approach was used).

End point type	Secondary

End point timeframe:

Up to Week 14 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	170		
Units: Percentage of participants				
number (not applicable)	19.1	50.0		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The Mantel Haenszel analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation)

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [3]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-31.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.9
upper limit	-22.6

Notes:

[3] - Nominal 1-sided p-value

Secondary: Percentage of Participants with CMV End-organ Disease up to Week 24 Post-transplant

End point title	Percentage of Participants with CMV End-organ Disease up to Week 24 Post-transplant

End point description:

CMV end-organ disease met per-protocol diagnostic criteria for CMV-pneumonia, gastrointestinal disease, hepatitis, central nervous system disease, retinitis, nephritis, cystitis, myocarditis, pancreatitis, or other disease categories. Only Clinical Adjudication Committee-confirmed CMV end-organ disease was included in this analysis. The percentage of participants with CMV end-organ disease was assessed. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated. A participant with a missing value was excluded from the analysis (i.e., Data as observed [DAO] approach was used).

End point type	Secondary

End point timeframe:

Up to Week 24 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	123		
Units: Percentage of participants				
number (not applicable)	2.0	2.4		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The Mantel Haenszel analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation)

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4056 [4]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	3.2

Notes:

[4] - Nominal 1-sided p-value

Secondary: Percentage of Participants with CMV End-organ Disease up to Week 14 Post-transplant

End point title	Percentage of Participants with CMV End-organ Disease up to Week 14 Post-transplant

End point description:

CMV end-organ disease met per-protocol diagnostic criteria for CMV-pneumonia, gastrointestinal disease, hepatitis, central nervous system disease, retinitis, nephritis, cystitis, myocarditis, pancreatitis, or other disease categories. Only Clinical Adjudication Committee-confirmed CMV end-organ disease was included in this analysis. The percentage of participants with CMV end-organ disease was assessed. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated. A participant with a missing value was excluded from the analysis (i.e., DAO approach was used).

End point type	Secondary

End point timeframe:

Up to Week 14 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	145		
Units: Percentage of participants				
number (not applicable)	0.4	1.4		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The Mantel Haenszel analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation)

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2258 [5]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	1.5

Notes:

[5] - Nominal 1-sided p-value

Secondary: Percentage of Participants with Pre-emptive Therapy for CMV Viremia up to Week 14 Post-transplant

End point title	Percentage of Participants with Pre-emptive Therapy for CMV Viremia up to Week 14 Post-transplant

End point description:

Initiation of anti-CMV pre-emptive therapy was based on documented CMV viremia and the clinical condition of the participant. The percentage of participants with initiation of anti-CMV pre-emptive anti-CMV therapy was assessed. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated. Participants who prematurely discontinued from the study or had a missing outcome through the 14-week visit window were considered treatment failure (i.e. NC=F approach was used).

End point type	Secondary

End point timeframe:

Up to Week 14 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	170		
Units: Percentage of participants				
number (not applicable)	18.8	49.4		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The Mantel Haenszel analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation)

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [6]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.6
upper limit	-22.4

Notes:

[6] - Nominal 1-sided p-value

Secondary: Percentage of Participants with Pre-emptive Therapy for CMV Viremia up to Week 24 Post-transplant

End point title	Percentage of Participants with Pre-emptive Therapy for CMV Viremia up to Week 24 Post-transplant

End point description:

Initiation of anti-CMV pre-emptive therapy was based on documented CMV viremia and the clinical condition of the participant. The percentage of participants with initiation of anti-CMV pre-emptive anti-CMV therapy was assessed. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated. Participants who prematurely discontinued from the study or had a missing outcome through the 24-week visit window were considered treatment failure (i.e. NC=F approach was used).

End point type	Secondary

End point timeframe:

Up to Week 24 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	170		
Units: Percentage of participants				
number (not applicable)	36.6	59.4		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The Mantel Haenszel analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation)

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [7]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-23.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.3
upper limit	-14.3

Notes:

[7] - Nominal 1-sided p-value

Secondary: Time to Initiation of Pre-emptive Therapy for CMV Viremia (Kaplan-

Meier Estimate of Percentage of Participants with a Qualifying Event at Week 24 Post-transplant)

End point title	Time to Initiation of Pre-emptive Therapy for CMV Viremia (Kaplan-Meier Estimate of Percentage of Participants with a Qualifying Event at Week 24 Post-transplant)

End point description:

The need for anti-CMV pre-emptive therapy was based on documented CMV viremia and the clinical condition of the participant. The outcome was calculated from the day of transplantation to the start of anti-CMV pre-emptive therapy, and was analyzed by the Kaplan-Meier method. Participants were censored at the last assessment for participants who discontinued or did not initiate pre-emptive therapy. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated.

End point type	Secondary

End point timeframe:

Up to Week 24 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	170		
Units: Percentage of participants				
number (confidence interval 95%)	17.2 (12.8 to 21.6)	42.4 (34.7 to 50.2)		

Statistical analyses

Statistical analysis title	Log Rank

Statistical analysis description:

The log rank test analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation)

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [8]
Method	Logrank

Notes:

[8] - Nominal 2-sided p-value

Other pre-specified: Percentage of Participants with One or More Adverse Events up to Week 48 Post-transplant

End point title	Percentage of Participants with One or More Adverse Events up to Week 48 Post-transplant

End point description:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor’s product, is also an adverse event. The All Subjects as Treated population (ASaT) was all

randomized participants who received at least one dose of study medication.

End point type	Other pre-specified

End point timeframe:

Up to Week 48 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	192		
Units: Percentage of participants				
number (not applicable)	98.4	100.0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants Discontinued from Study Medication Due to an Adverse Event

End point title	Percentage of Participants Discontinued from Study Medication Due to an Adverse Event

End point description:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor’s product, is also an adverse event. The ASaT was all randomized participants who received at least one dose of study medication.

End point type	Other pre-specified

End point timeframe:

Up to Week 14 post-transplant

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	192		
Units: Percentage of participants				
number (not applicable)	19.6	51.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Week 48 post-transplant	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Letermovir
Reporting group description:	
Letermovir oral or intravenous (IV) formulation was administered once daily for up to 14 weeks, beginning up to Day 28 post-transplant. The dose was 240 mg once daily for participants receiving concomitant cyclosporin A and 480 mg once daily for participants not receiving cyclosporin A. Intravenous infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets.	
Reporting group title	Placebo
Reporting group description:	
Placebo oral or IV formulation was administered once daily for up to 14 weeks, beginning up to Day 28 post-transplant. The number of placebo tablets was to mimic that for letermovir administration according to the concomitant cyclosporin A status. Intravenous infusion was administered only to participants who are unable to swallow tablets or who have a condition that may interfere with absorption of the tablets.	

Serious adverse events	Letermovir	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	202 / 373 (54.16%)	115 / 192 (59.90%)	
number of deaths (all causes)	81	47	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	6 / 373 (1.61%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Acute myeloid leukaemia			

subjects affected / exposed	7 / 373 (1.88%)	4 / 192 (2.08%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 3	
Acute myeloid leukaemia recurrent			
subjects affected / exposed	23 / 373 (6.17%)	17 / 192 (8.85%)	
occurrences causally related to treatment / all	0 / 23	0 / 17	
deaths causally related to treatment / all	0 / 15	0 / 11	
B-cell lymphoma recurrent			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia recurrent			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diffuse large B-cell lymphoma recurrent			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Mantle cell lymphoma			

subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Mantle cell lymphoma recurrent			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycosis fungoides			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mycosis fungoides recurrent			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	2 / 373 (0.54%)	3 / 192 (1.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Natural killer-cell leukaemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-Hodgkin's lymphoma recurrent			
subjects affected / exposed	0 / 373 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma recurrent			

subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Post transplant lymphoproliferative disorder			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Primary myelofibrosis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	3 / 373 (0.80%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive disease			
subjects affected / exposed	3 / 373 (0.80%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	2 / 373 (0.54%)	4 / 192 (2.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 3	
Pyrexia			
subjects affected / exposed	10 / 373 (2.68%)	4 / 192 (2.08%)	
occurrences causally related to treatment / all	0 / 12	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	45 / 373 (12.06%)	29 / 192 (15.10%)	
occurrences causally related to treatment / all	0 / 49	0 / 31	
deaths causally related to treatment / all	0 / 9	0 / 7	
Transplant rejection			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse alveolar damage			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	0 / 373 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	2 / 373 (0.54%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 373 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	7 / 373 (1.88%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Tonsillar disorder			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	0 / 373 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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			
Allergic transfusion reaction			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed engraftment			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fractured sacrum			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 373 (0.00%)	3 / 192 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion-related acute lung injury			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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	3 / 373 (0.80%)	3 / 192 (1.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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			
Cerebral haemorrhage			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Encephalopathy			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	3 / 373 (0.80%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurotoxicity			
subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	7 / 373 (1.88%)	3 / 192 (1.56%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukopenia			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	3 / 373 (0.80%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 373 (1.07%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 373 (0.80%)	5 / 192 (2.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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	3 / 373 (0.80%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 373 (0.54%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stomatitis haemorrhagic			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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 / 373 (0.80%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	2 / 373 (0.54%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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 / 373 (0.54%)	3 / 192 (1.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Skin and subcutaneous tissue disorders			
Rash generalised			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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	7 / 373 (1.88%)	9 / 192 (4.69%)	
occurrences causally related to treatment / all	0 / 7	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cystitis haemorrhagic			
subjects affected / exposed	3 / 373 (0.80%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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			
Arthralgia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibromyalgia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture pain			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adenoviral haemorrhagic cystitis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 373 (0.27%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atypical pneumonia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 373 (0.54%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
BK virus infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchiolitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	4 / 373 (1.07%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cellulitis			
subjects affected / exposed	3 / 373 (0.80%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral toxoplasmosis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium bacteraemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	3 / 373 (0.80%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 373 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis viral			
subjects affected / exposed	1 / 373 (0.27%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	14 / 373 (3.75%)	15 / 192 (7.81%)	
occurrences causally related to treatment / all	0 / 15	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr viraemia			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	3 / 373 (0.80%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fusarium infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 373 (0.54%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
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 / 373 (0.27%)	0 / 192 (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	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal candidiasis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site cellulitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis viral			

subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucormycosis			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	15 / 373 (4.02%)	6 / 192 (3.13%)	
occurrences causally related to treatment / all	0 / 15	0 / 6	
deaths causally related to treatment / all	0 / 7	0 / 2	
Pneumonia adenoviral			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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	3 / 373 (0.80%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia staphylococcal			

subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia viral			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas bronchitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 373 (0.27%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinitis viral			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	2 / 373 (0.54%)	0 / 192 (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	8 / 373 (2.14%)	4 / 192 (2.08%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 6	0 / 3	
Septic shock			
subjects affected / exposed	5 / 373 (1.34%)	7 / 192 (3.65%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 4	0 / 3	
Sinusitis			
subjects affected / exposed	4 / 373 (1.07%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	4 / 373 (1.07%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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	4 / 373 (1.07%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	3 / 373 (0.80%)	3 / 192 (1.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral haemorrhagic cystitis			
subjects affected / exposed	3 / 373 (0.80%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 373 (0.27%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gout			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 373 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactose intolerance			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tetany			
subjects affected / exposed	1 / 373 (0.27%)	0 / 192 (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	Letermovir	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	360 / 373 (96.51%)	186 / 192 (96.88%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	34 / 373 (9.12%)	23 / 192 (11.98%)	
occurrences (all)	38	24	
Hypotension			
subjects affected / exposed	16 / 373 (4.29%)	11 / 192 (5.73%)	
occurrences (all)	16	13	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	29 / 373 (7.77%)	9 / 192 (4.69%)	
occurrences (all)	36	13	
Chest pain			
subjects affected / exposed	20 / 373 (5.36%)	5 / 192 (2.60%)	
occurrences (all)	21	5	
Fatigue			
subjects affected / exposed	55 / 373 (14.75%)	26 / 192 (13.54%)	
occurrences (all)	63	30	
Mucosal inflammation			
subjects affected / exposed	45 / 373 (12.06%)	24 / 192 (12.50%)	
occurrences (all)	47	24	
Oedema peripheral			
subjects affected / exposed	60 / 373 (16.09%)	23 / 192 (11.98%)	
occurrences (all)	74	27	
Pyrexia			
subjects affected / exposed	85 / 373 (22.79%)	50 / 192 (26.04%)	
occurrences (all)	112	60	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	147 / 373 (39.41%)	74 / 192 (38.54%)	
occurrences (all)	173	91	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	62 / 373 (16.62%)	27 / 192 (14.06%)	
occurrences (all)	70	28	
Dyspnoea			
subjects affected / exposed	36 / 373 (9.65%)	9 / 192 (4.69%)	
occurrences (all)	38	10	
Epistaxis			
subjects affected / exposed	25 / 373 (6.70%)	13 / 192 (6.77%)	
occurrences (all)	29	13	
Oropharyngeal pain			
subjects affected / exposed	32 / 373 (8.58%)	19 / 192 (9.90%)	
occurrences (all)	34	20	
Rhinorrhoea			

subjects affected / exposed	15 / 373 (4.02%)	10 / 192 (5.21%)	
occurrences (all)	18	11	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	23 / 373 (6.17%)	5 / 192 (2.60%)	
occurrences (all)	23	5	
Insomnia			
subjects affected / exposed	35 / 373 (9.38%)	12 / 192 (6.25%)	
occurrences (all)	37	12	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 373 (6.97%)	17 / 192 (8.85%)	
occurrences (all)	31	20	
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 373 (5.63%)	13 / 192 (6.77%)	
occurrences (all)	24	16	
Blood creatinine increased			
subjects affected / exposed	39 / 373 (10.46%)	14 / 192 (7.29%)	
occurrences (all)	43	17	
Nervous system disorders			
Dizziness			
subjects affected / exposed	29 / 373 (7.77%)	16 / 192 (8.33%)	
occurrences (all)	30	16	
Dysgeusia			
subjects affected / exposed	19 / 373 (5.09%)	10 / 192 (5.21%)	
occurrences (all)	19	10	
Headache			
subjects affected / exposed	58 / 373 (15.55%)	24 / 192 (12.50%)	
occurrences (all)	68	26	
Tremor			
subjects affected / exposed	29 / 373 (7.77%)	13 / 192 (6.77%)	
occurrences (all)	30	14	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 373 (6.43%)	12 / 192 (6.25%)	
occurrences (all)	39	13	

Febrile neutropenia			
subjects affected / exposed	28 / 373 (7.51%)	19 / 192 (9.90%)	
occurrences (all)	28	20	
Neutropenia			
subjects affected / exposed	18 / 373 (4.83%)	11 / 192 (5.73%)	
occurrences (all)	20	12	
Thrombocytopenia			
subjects affected / exposed	27 / 373 (7.24%)	13 / 192 (6.77%)	
occurrences (all)	32	13	
Eye disorders			
Dry eye			
subjects affected / exposed	24 / 373 (6.43%)	12 / 192 (6.25%)	
occurrences (all)	24	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	49 / 373 (13.14%)	19 / 192 (9.90%)	
occurrences (all)	53	21	
Abdominal pain upper			
subjects affected / exposed	23 / 373 (6.17%)	17 / 192 (8.85%)	
occurrences (all)	30	20	
Constipation			
subjects affected / exposed	30 / 373 (8.04%)	22 / 192 (11.46%)	
occurrences (all)	30	24	
Diarrhoea			
subjects affected / exposed	108 / 373 (28.95%)	51 / 192 (26.56%)	
occurrences (all)	139	64	
Dry mouth			
subjects affected / exposed	21 / 373 (5.63%)	11 / 192 (5.73%)	
occurrences (all)	22	11	
Dyspepsia			
subjects affected / exposed	21 / 373 (5.63%)	6 / 192 (3.13%)	
occurrences (all)	22	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 373 (1.61%)	11 / 192 (5.73%)	
occurrences (all)	6	11	
Nausea			

subjects affected / exposed	106 / 373 (28.42%)	53 / 192 (27.60%)	
occurrences (all)	141	64	
Stomatitis			
subjects affected / exposed	24 / 373 (6.43%)	14 / 192 (7.29%)	
occurrences (all)	25	14	
Vomiting			
subjects affected / exposed	79 / 373 (21.18%)	35 / 192 (18.23%)	
occurrences (all)	93	40	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	31 / 373 (8.31%)	16 / 192 (8.33%)	
occurrences (all)	32	19	
Erythema			
subjects affected / exposed	34 / 373 (9.12%)	12 / 192 (6.25%)	
occurrences (all)	37	13	
Pruritus			
subjects affected / exposed	31 / 373 (8.31%)	12 / 192 (6.25%)	
occurrences (all)	35	14	
Rash			
subjects affected / exposed	90 / 373 (24.13%)	51 / 192 (26.56%)	
occurrences (all)	109	62	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	35 / 373 (9.38%)	22 / 192 (11.46%)	
occurrences (all)	37	25	
Dysuria			
subjects affected / exposed	17 / 373 (4.56%)	11 / 192 (5.73%)	
occurrences (all)	17	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	30 / 373 (8.04%)	15 / 192 (7.81%)	
occurrences (all)	31	18	
Back pain			
subjects affected / exposed	24 / 373 (6.43%)	20 / 192 (10.42%)	
occurrences (all)	26	22	
Muscle spasms			

subjects affected / exposed	12 / 373 (3.22%)	10 / 192 (5.21%)	
occurrences (all)	13	12	
Myalgia			
subjects affected / exposed	21 / 373 (5.63%)	4 / 192 (2.08%)	
occurrences (all)	21	4	
Pain in extremity			
subjects affected / exposed	20 / 373 (5.36%)	16 / 192 (8.33%)	
occurrences (all)	24	17	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	21 / 373 (5.63%)	4 / 192 (2.08%)	
occurrences (all)	24	5	
Cytomegalovirus infection			
subjects affected / exposed	55 / 373 (14.75%)	77 / 192 (40.10%)	
occurrences (all)	65	93	
Nasopharyngitis			
subjects affected / exposed	19 / 373 (5.09%)	8 / 192 (4.17%)	
occurrences (all)	22	8	
Viraemia			
subjects affected / exposed	12 / 373 (3.22%)	12 / 192 (6.25%)	
occurrences (all)	12	12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 373 (11.53%)	26 / 192 (13.54%)	
occurrences (all)	48	26	
Hyperglycaemia			
subjects affected / exposed	31 / 373 (8.31%)	13 / 192 (6.77%)	
occurrences (all)	31	14	
Hyperkalaemia			
subjects affected / exposed	28 / 373 (7.51%)	5 / 192 (2.60%)	
occurrences (all)	29	5	
Hypokalaemia			
subjects affected / exposed	23 / 373 (6.17%)	12 / 192 (6.25%)	
occurrences (all)	25	13	
Hypomagnesaemia			

subjects affected / exposed	24 / 373 (6.43%)	15 / 192 (7.81%)	
occurrences (all)	24	16	
Hyponatraemia			
subjects affected / exposed	23 / 373 (6.17%)	10 / 192 (5.21%)	
occurrences (all)	24	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2014	Amendment 001: Changes to plasma collection times, clarification that plasma sampling for CMV DNA polymerase chain reaction (PCR) testing was to be confirmatory, change to definition of documented viremia on a confirmatory sample, and revision of guidance regarding viral load threshold for initiation of pre-emptive therapy.
01 September 2014	Amendment 002: Added an exclusion criterion to define and exclude participants of Asian descent, change to allow a participant to reinitiate protocol-defined study therapy under the instance where the confirmatory central laboratory test result for CMV DNA PCR obtained on the day of pre-emptive therapy initiation is negative and pre-emptive therapy is stopped.
16 March 2015	Amendment 003: Addition of a 480-mg oral tablet formulation of letermovir, and removal of the exclusion criterion that excluded participants of Asian descent.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported