Clinical trial results:
A Phase 3 randomized, double-blind, placebocontrolled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT)

Summary

EudraCT number	2018-001038-17
Trial protocol	GB DE ES FR IT
Global end of trial date	16 March 2022

Results information

Result version number	v1 (current)
This version publication date	15 March 2023
First version publication date	15 March 2023

Trial information

Trial identification

Sponsor protocol code	8228-040

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03930615
WHO universal trial number (UTN)	-
Other trial identifiers	Merck: MK-8228-040

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue,, Rahway, NJ, United States, P.O. Box 2000
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, 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	16 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2021
Global end of trial reached?	Yes
Global end of trial date	16 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of letermovir (LET) versus placebo when cytomegalovirus (CMV) prophylaxis was extended from 100 days to 200 days post-transplant in CMV seropositive participants who received an allogenic hematopoietic stem cell transplant (HSCT). It was hypothesized that LET is superior to placebo in the prevention of clinically-significant CMV infection when LET prophylaxis is extended from 100 to 200 days.

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	21 June 2019
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	France: 28
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Italy: 61
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	220
EEA total number of subjects	119

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)	176
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Cytomegalovirus (CMV)-seropositive recipients (R+) of a hematopoietic stem cell transplant (HSCT) who had received letermovir (LET) prophylaxis through Week 14 (~100 days) post-transplant and were at high risk for CMV infection and/or disease were enrolled in this study.

Period 1

Period 1 title	Randomized
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Letermovir

Arm description:

Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of LET (480 mg once daily alone or 240 mg once daily for participants on cyclosporin A) treatment.

Arm type	Experimental
Investigational medicinal product name	Letermovir
Investigational medicinal product code	
Other name	PREVYMIS™, MK-8228
Pharmaceutical forms	Buccal tablet, Infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Participants who received hematopoietic stem cell transplant (HSCT) transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of LET (480 mg once daily alone or 240 mg once daily for participants on cyclosporin A) treatment.

Arm title	Placebo

Arm description:

Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of placebo treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet, Infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of placebo treatment (inactive saline or dextrose).

Number of subjects in period 1	Letermovir	Placebo
Started	145	75
Completed	144	74
Not completed	1	1
Not treated	1	1

Period 2

Period 2 title	Treated
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Letermovir

Arm description:

Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of LET (480 mg once daily alone or 240 mg once daily for participants on cyclosporin A) treatment.

Arm type	Experimental
Investigational medicinal product name	Letermovir
Investigational medicinal product code	
Other name	PREVYMIS™, MK-8228
Pharmaceutical forms	Buccal tablet, Infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Participants who received hematopoietic stem cell transplant (HSCT) transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of LET (480 mg once daily alone or 240 mg once daily for participants on cyclosporin A) treatment.

Arm title	Placebo

Arm description:

Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of placebo treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet, Infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of placebo treatment (inactive saline or dextrose).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Instead of the randomized/enrolled population in period 1, the baseline period was the treated population in period 2.

Number of subjects in period 2[2]	Letermovir	Placebo
Started	144	74
Completed	118	63
Not completed	26	11
Adverse event, serious fatal	9	3
Physician decision	3	4
Consent withdrawn by subject	13	2
Lost to follow-up	1	2

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number randomized/enrolled in the trial was different from the number at baseline, which was the treated population.

Baseline characteristics

Reporting groups	
Reporting group title	Letermovir
Reporting group description:	
Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of LET (480 mg once daily alone or 240 mg once daily for participants on cyclosporin A) treatment.	
Reporting group title	Placebo
Reporting group description:	
Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of placebo treatment.	

Reporting group values	Letermovir	Placebo	Total
Number of subjects	144	74	218
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)	112	63	175
From 65-84 years	32	11	43
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.9	62.7	
standard deviation	± 14.3	± 12.9	-
Sex: Female, Male Units: Participants			
Female	52	31	83
Male	92	43	135
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	16	8	24
Native Hawaiian or Other Pacific Islander	2	0	2
Black or African American	3	1	4
White	113	60	173
More than one race	2	1	3
Unknown or Not Reported	8	4	12
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	13	8	21
Not Hispanic or Latino	106	53	159
Unknown or Not Reported	25	13	38

Donor Stratum Units: Subjects			
Haploidentical	45	22	67
Non-haploidentical	99	52	151

End points

End points reporting groups

Reporting group title	Letermovir
Reporting group description:	
Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of LET (480 mg once daily alone or 240 mg once daily for participants on cyclosporin A) treatment.	
Reporting group title	Placebo
Reporting group description:	
Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of placebo treatment.	
Reporting group title	Letermovir
Reporting group description:	
Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of LET (480 mg once daily alone or 240 mg once daily for participants on cyclosporin A) treatment.	
Reporting group title	Placebo
Reporting group description:	
Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of placebo treatment.	

Primary: Percentage of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant

End point title	Percentage of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant
End point description:	
Clinically significant CMV infection is either the onset of probable or proven CMV end-organ disease or initiation of anti-CMV preemptive therapy (PET) with approved anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) based on documented CMV viremia and the clinical condition of the participant. Missing values were handled by the observed failure (OF) approach where failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with CMV viremia from week 14 (~100 days) through week 28 post-transplant. It was hypothesized that LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days. The population analyzed was all randomized participants who received at least 1 dose of study intervention.	
End point type	Primary
End point timeframe:	
From Week 14 post-transplant to Week 28 post-transplant (approximately 14 weeks)	

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	2.8	18.9		

Statistical analyses

Statistical analysis title	Treatment differences in percent response

Statistical analysis description:

It was hypothesized that LET is superior to placebo in the prevention of clinically significant CMV infection.

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0005 [2]
Method	Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.8
upper limit	-6.5

Notes:

[1] - 95% CIs for the treatment differences in percent response were calculated using stratum adjusted Mantel Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).
[2] - A one-sided p-value ≤0.0249 was used for declaring statistical significance

Secondary: Percentage of participants experiencing ≥1 adverse events (AEs) from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant

End point title	Percentage of participants experiencing ≥1 adverse events (AEs) from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The population analyzed was all randomized participants who received at least 1 dose of study intervention according to the study intervention they received.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 28 post-transplant (approximately 14 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	88.9	93.2		

Statistical analyses

Statistical analysis title	Difference in Percentage
Statistical analysis description: Miettinen & Nurminen method	
Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Difference in Percentage
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	4.7

Notes:

[3] - Letermovir minus Placebo

Secondary: Percentage of participants withdrawing from study drug due to an AE from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant

End point title	Percentage of participants withdrawing from study drug due to an AE from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The population analyzed was all randomized participants who received at least 1 dose of study intervention according to the study intervention they received.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 28 post-transplant (approximately 14 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	4.9	1.4		

Statistical analyses

Statistical analysis title	Difference in Percentage
Statistical analysis description: Miettinen & Nurminen method	
Comparison groups	Letermovir v Placebo

Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Difference in Percentage
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	8.6

Notes:

[4] - Letermovir minus placebo

Secondary: Time to onset of clinically significant CMV infection from Week 14 post-transplant to Week 28 post-transplant

End point title	Time to onset of clinically significant CMV infection from Week 14 post-transplant to Week 28 post-transplant

End point description:

Clinically significant CMV infection is either the onset of probable or proven CMV end-organ disease or initiation of anti-CMV PET with approved anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) based on documented CMV viremia and the clinical condition of the participant. Time to onset of clinically significant CMV infection is the elapsed time from transplant to the onset of CMV end-organ disease or to the initiation of anti-CMV PET. Time to onset was determined from the Kaplan-Meier method for censored data. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 28 post-transplant (approximately 14 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[5]	74[6]		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[5] - 9999 means the median time was not reached.

[6] - 9999 means the median time was not reached.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinically significant CMV infection from Week 14 post-transplant through Week 48 post-transplant

End point title	Percentage of participants with clinically significant CMV infection from Week 14 post-transplant through Week 48 post-transplant

End point description:

Clinically significant CMV infection is either the onset of probable or proven CMV end-organ disease or initiation of anti-CMV PET with approved anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) based on documented CMV viremia and the clinical condition of the participant. Missing values

were handled by the OF approach where failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with CMV viremia from week 14 (~100 days) through week 48 post-transplant. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 48 post-transplant (approximately 34 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	14.6	20.3		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Mantel Haenszel method

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1591
Method	Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8
upper limit	5.4

Notes:

[7] - 95% CIs for the treatment differences in percent response were calculated using stratum adjusted Mantel Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).

Secondary: Percentage of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant

End point title	Percentage of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant

End point description:

Clinically significant CMV infection is either the onset of probable or proven CMV end-organ disease or initiation of anti-CMV PET with approved anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) based on documented CMV viremia and the clinical condition of the participant. Missing values were handled by the OF approach where failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with CMV viremia from week 14 (~100 days) through week 38 post-transplant. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 38 post-transplant (approximately 24 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	14.6	20.3		

Statistical analyses

Statistical analysis title	Difference in Percentage

Statistical analysis description:

Mantel Haenszel method

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.1591
Method	Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8
upper limit	5.4

Notes:

[8] - 95% CIs for the treatment differences in percent response were calculated using stratum adjusted Mantel Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).

Secondary: Time to onset of clinically significant CMV infection from Week 14 post-transplant to Week 48 post-transplant

End point title	Time to onset of clinically significant CMV infection from Week 14 post-transplant to Week 48 post-transplant

End point description:

Clinically significant CMV infection is either the onset of probable or proven CMV end-organ disease or initiation of anti-CMV PET with approved anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) based on documented CMV viremia and the clinical condition of the participant. Time to onset of clinically significant CMV infection is the elapsed time from transplant to the onset of CMV end-organ disease or to the initiation of anti-CMV PET. Time to onset was determined from the Kaplan-Meier method for censored data. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 48 post-transplant (approximately 34 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[9]	74[10]		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[9] - 9999 means the median time was not reached.

[10] - 9999 means the median time was not reached.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with CMV viremia who started PET from Week 14 post-transplant to Week 48 post-transplant

End point title	Percentage of participants with CMV viremia who started PET from Week 14 post-transplant to Week 48 post-transplant

End point description:

The percentage of participants with CMV viremia who initiated PET of anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) was determined. Missing values were handled with the OF approach, where failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with CMV viremia from week 14 through week 48 post-transplant. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 48 post-transplant (approximately 34 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	13.2	18.9		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Mantel Haenszel method

Comparison groups	Letermovir v Placebo

Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.1494
Method	Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	5.1

Notes:

[11] - 95% CIs for the treatment differences in percent response were calculated using stratum adjusted Mantel Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).

Secondary: Percentage of participants with CMV viremia who started PET from Week 14 post-transplant to Week 28 post-transplant

End point title	Percentage of participants with CMV viremia who started PET from Week 14 post-transplant to Week 28 post-transplant

End point description:

The percentage of participants with CMV viremia who initiated PET of anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) was determined. Missing values were handled with the OF approach, where failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with CMV viremia from week 14 through week 28 post-transplant. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 28 post-transplant (approximately 14 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	2.1	16.2		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Mantel Haenszel method

Comparison groups	Letermovir v Placebo

Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.0012
Method	Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	-14.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.3
upper limit	-5

Notes:

[12] - 95% CIs for the treatment differences in percent response were calculated using stratum adjusted Mantel Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).

Secondary: Percentage of participants with all-cause mortality from Week 14 post-transplant to Week 48 post-transplant

End point title	Percentage of participants with all-cause mortality from Week 14 post-transplant to Week 48 post-transplant

End point description:

The percentage of participants who died due to any cause (all-cause mortality) from Week 14 to Week 48 was determined. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 48 post-transplant (approximately 34 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	8.3	8.1		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Mantel Haenszel method

Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.5264
Method	Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	8.4

Notes:

[13] - 95% CIs for the treatment differences in percent response were calculated using stratum adjusted Mantel Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).

Secondary: Percentage of participants with all-cause mortality from Week 14 post-transplant to Week 28 post-transplant

End point title	Percentage of participants with all-cause mortality from Week 14 post-transplant to Week 28 post-transplant

End point description:

The percentage of participants who died due to any cause (all-cause mortality) from Week 14 to Week 28 was determined. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 28 post-transplant (approximately 14 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	74		
Units: Percentage of participants				
number (not applicable)	2.1	1.4		

Statistical analyses

Statistical analysis title	Treatment Difference
Statistical analysis description:	
Mantel Haenszel method	
Comparison groups	Letermovir v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.6244
Method	Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	5.3

Notes:

[14] - 95% CIs for the treatment differences in percent response were calculated using stratum adjusted Mantel Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).

Secondary: Time to all-cause mortality from Week 14 post-transplant to Week 28 post-transplant

End point title	Time to all-cause mortality from Week 14 post-transplant to Week 28 post-transplant

End point description:

Time to all-cause mortality is the time elapsed after Week 14 post-transplant and death due to any cause, and was determined from the Kaplan-Meier method for censored data. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 28 post-transplant (approximately 14 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[15]	74[16]		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[15] - 9999 means there was insufficient time to reach a median survival time.

[16] - 9999 means there was insufficient time to reach a median survival time.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to all-cause mortality from Week 14 post-transplant to Week 48 post-transplant

End point title	Time to all-cause mortality from Week 14 post-transplant to Week 48 post-transplant

End point description:

Time to all-cause mortality is the time elapsed after Week 14 post-transplant and death due to any cause, and was determined from the Kaplan-Meier method for censored data. The population analyzed was all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From Week 14 post-transplant to Week 48 post-transplant (approximately 34 weeks)

End point values	Letermovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[17]	74[18]		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[17] - 9999 means there was insufficient time to reach a median survival time.

[18] - 9999 means there was insufficient time to reach a median survival time.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and serious.adverse events (SAEs): From 14 weeks post-transplant up to 48 weeks post-transplant (approximately 34 weeks); adverse events (AEs): From 14 weeks post-transplant up to 30 weeks post-transplant (approximately 16 weeks).

Adverse event reporting additional description:

The population analyzed for all-cause mortality (death due to any cause) was all randomized participants. The population analyzed for AEs was all randomized participants who received at least 1 dose of study intervention according to the study intervention they received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of placebo treatment

Reporting group title	Letermovir

Reporting group description:

Participants who received HSCT transplant and 100 days of LET prophylaxis were randomized to an additional 100 days of LET (480 mg once daily alone or 240 mg once daily for participants on cyclosporin A) treatment.

Serious adverse events	Placebo	Letermovir	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 74 (36.49%)	49 / 144 (34.03%)	
number of deaths (all causes)	8	16	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphoma			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large granular lymphocytosis			

subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chloroma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia recurrent			
subjects affected / exposed	3 / 74 (4.05%)	8 / 144 (5.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 3	0 / 6	
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	0 / 74 (0.00%)	2 / 144 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral T-cell lymphoma unspecified recurrent			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Plasma cell myeloma recurrent			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 74 (1.35%)	2 / 144 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pyrexia			
subjects affected / exposed	1 / 74 (1.35%)	4 / 144 (2.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	6 / 74 (8.11%)	9 / 144 (6.25%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Escherichia test positive			

subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (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			
Subdural haematoma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Guillain-Barre syndrome			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (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			
Thrombotic microangiopathy			
subjects affected / exposed	2 / 74 (2.70%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pure white cell aplasia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumatosis intestinalis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (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	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 74 (0.00%)	2 / 144 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			

subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoviral haemorrhagic cystitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 74 (1.35%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 74 (2.70%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 74 (2.70%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			

subjects affected / exposed	2 / 74 (2.70%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection reactivation			

subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral toxoplasmosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
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 / 74 (0.00%)	1 / 144 (0.69%)	
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 / 74 (0.00%)	1 / 144 (0.69%)	
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 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection fungal			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node tuberculosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			

subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 74 (6.76%)	4 / 144 (2.78%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (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	0 / 74 (0.00%)	2 / 144 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			

subjects affected / exposed	1 / 74 (1.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 74 (1.35%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rhinovirus infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 74 (2.70%)	2 / 144 (1.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	2 / 74 (2.70%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 74 (1.35%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoproteinaemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 144 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Letermovir	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 74 (78.38%)	100 / 144 (69.44%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	4 / 74 (5.41%)	4 / 144 (2.78%)	
occurrences (all)	6	4	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 74 (5.41%)	5 / 144 (3.47%)	
occurrences (all)	5	5	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 74 (5.41%)	10 / 144 (6.94%)	
occurrences (all)	4	11	
Dizziness			

subjects affected / exposed	4 / 74 (5.41%)	3 / 144 (2.08%)	
occurrences (all)	5	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 74 (4.05%)	8 / 144 (5.56%)	
occurrences (all)	3	9	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 74 (12.16%)	12 / 144 (8.33%)	
occurrences (all)	13	13	
Oedema peripheral			
subjects affected / exposed	9 / 74 (12.16%)	12 / 144 (8.33%)	
occurrences (all)	10	12	
Fatigue			
subjects affected / exposed	5 / 74 (6.76%)	5 / 144 (3.47%)	
occurrences (all)	5	6	
Oedema			
subjects affected / exposed	4 / 74 (5.41%)	0 / 144 (0.00%)	
occurrences (all)	4	0	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	22 / 74 (29.73%)	45 / 144 (31.25%)	
occurrences (all)	34	61	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 74 (4.05%)	9 / 144 (6.25%)	
occurrences (all)	4	10	
Nausea			
subjects affected / exposed	15 / 74 (20.27%)	17 / 144 (11.81%)	
occurrences (all)	17	19	
Diarrhoea			
subjects affected / exposed	11 / 74 (14.86%)	16 / 144 (11.11%)	
occurrences (all)	12	19	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			

subjects affected / exposed	6 / 74 (8.11%)	9 / 144 (6.25%)	
occurrences (all)	7	10	
Cough			
subjects affected / exposed	9 / 74 (12.16%)	8 / 144 (5.56%)	
occurrences (all)	11	8	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 74 (2.70%)	11 / 144 (7.64%)	
occurrences (all)	3	11	
Rash			
subjects affected / exposed	8 / 74 (10.81%)	9 / 144 (6.25%)	
occurrences (all)	8	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 74 (6.76%)	6 / 144 (4.17%)	
occurrences (all)	5	6	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	4 / 74 (5.41%)	3 / 144 (2.08%)	
occurrences (all)	4	4	
Cytomegalovirus infection reactivation			
subjects affected / exposed	5 / 74 (6.76%)	6 / 144 (4.17%)	
occurrences (all)	6	6	
Upper respiratory tract infection			
subjects affected / exposed	5 / 74 (6.76%)	6 / 144 (4.17%)	
occurrences (all)	5	7	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	4 / 74 (5.41%)	5 / 144 (3.47%)	
occurrences (all)	4	5	
Decreased appetite			
subjects affected / exposed	11 / 74 (14.86%)	6 / 144 (4.17%)	
occurrences (all)	13	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2019	Amendment 01: Added the requirement that the intravenous (IV) formulation of letermovir (LET) supplied by the Sponsor to sites as study medication must be administered through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials.
05 February 2020	Amendment 02: Limited enrollment of participants who have anti-thymocyte globulin as the only high-risk category for CMV reactivation to =< 20% of the total trial population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported