



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

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