



Clinical trial results:

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

Summary

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

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 19 October 2017 |
| First version publication date | 19 October 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 8228-001 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 November 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 06 June 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 482 |
| From 65 to 84 years | 88 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Letermovir |

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

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

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Letermovir |
|-----------------------|------------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

| | |
|---|----------------------|
| Statistical analysis title | Risk Difference |
| Statistical analysis description: The Mantel Haenszel analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation) | |
| Comparison groups | Letermovir v Placebo |

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

Notes:

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

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

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

End point description:

Time to onset of clinically-significant CMV infection was defined from the day of transplantation to the day the participant developed clinically-significant CMV infection, and was analyzed by the Kaplan-Meier method. Participants were censored at the last assessment for participants who discontinued or did not develop clinically-significant CMV infection. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 24 post-transplant

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

Statistical analyses

| | |
|---|---------------------|
| Statistical analysis title | Log Rank |
| Statistical analysis description: | |
| The log rank test was adjusted for sample size for each stratum (high or low risk for CMV reactivation) | |
| Comparison groups | Letemovir v Placebo |

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

Notes:

[2] - Nominal 2-sided p-value

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 14 post-transplant

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

Statistical analyses

| | |
|----------------------------|-----------------|
| Statistical analysis title | Risk Difference |
|----------------------------|-----------------|

Statistical analysis description:

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

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

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

Notes:

[3] - Nominal 1-sided p-value

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 24 post-transplant

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

Statistical analyses

| | |
|----------------------------|-----------------|
| Statistical analysis title | Risk Difference |
|----------------------------|-----------------|

Statistical analysis description:

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

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

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

Notes:

[4] - Nominal 1-sided p-value

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 14 post-transplant

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

Statistical analyses

| | |
|----------------------------|-----------------|
| Statistical analysis title | Risk Difference |
|----------------------------|-----------------|

Statistical analysis description:

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

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

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

Notes:

[5] - Nominal 1-sided p-value

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 14 post-transplant

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

Statistical analyses

| | |
|----------------------------|-----------------|
| Statistical analysis title | Risk Difference |
|----------------------------|-----------------|

Statistical analysis description:

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

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

Notes:

[6] - Nominal 1-sided p-value

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 24 post-transplant

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

Statistical analyses

| | |
|----------------------------|-----------------|
| Statistical analysis title | Risk Difference |
|----------------------------|-----------------|

Statistical analysis description:

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

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

Notes:

[7] - Nominal 1-sided p-value

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

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

| | |
|--|--|
| End point title | Time to Initiation of Pre-emptive Therapy for CMV Viremia (Kaplan-Meier Estimate of Percentage of Participants with a Qualifying Event at Week 24 Post-transplant) |
| End point description: The need for anti-CMV pre-emptive therapy was based on documented CMV viremia and the clinical condition of the participant. The outcome was calculated from the day of transplantation to the start of anti-CMV pre-emptive therapy, and was analyzed by the Kaplan-Meier method. Participants were censored at the last assessment for participants who discontinued or did not initiate pre-emptive therapy. The FAS was all randomized participants who received at least one dose of study drug and had no detectable CMV viral DNA on the day treatment was initiated. | |
| End point type | Secondary |
| End point timeframe: Up to Week 24 post-transplant | |

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

Statistical analyses

| | |
|---|----------------------|
| Statistical analysis title | Log Rank |
| Statistical analysis description: The log rank test analysis was adjusted for sample size for each stratum (high or low risk for CMV reactivation) | |
| Comparison groups | Letermovir v Placebo |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 [8] |
| Method | Logrank |

Notes:

[8] - Nominal 2-sided p-value

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

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

End point description:

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

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

| | |
|-------------------------------|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| Up to Week 48 post-transplant | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|-------------------------------|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| Up to Week 14 post-transplant | |

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 48 post-transplant

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

| | |
|-----------------------|------------|
| Reporting group title | Letermovir |
|-----------------------|------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 3 / 373 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 2 / 373 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Stomatitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 192 (0.52%) | 3 / 373 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 2 / 192 (1.04%) | 2 / 373 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venoocclusive liver disease | | | |
| subjects affected / exposed | 3 / 192 (1.56%) | 2 / 373 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Acute kidney injury | | | |
| subjects affected / exposed | 9 / 192 (4.69%) | 7 / 373 (1.88%) | |
| occurrences causally related to treatment / all | 1 / 11 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 2 / 192 (1.04%) | 3 / 373 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| 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 | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibromyalgia | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture pain | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myopathy | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Adenoviral haemorrhagic cystitis subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspergillus infection subjects affected / exposed | 2 / 192 (1.04%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atypical pneumonia subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bacteraemia subjects affected / exposed | 1 / 192 (0.52%) | 2 / 373 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| BK virus infection subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bronchiolitis subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| 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 | 1 / 192 (0.52%) | 4 / 373 (1.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 3 / 373 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis orbital | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral toxoplasmosis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium bacteriaemia | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 3 / 373 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 2 / 192 (1.04%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis viral | | | |
| subjects affected / exposed | 2 / 192 (1.04%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus infection | | | |

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonas bronchitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 373 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinitis viral | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 2 / 373 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 192 (2.08%) | 8 / 373 (2.14%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 6 | |
| Septic shock | | | |
| subjects affected / exposed | 7 / 192 (3.65%) | 5 / 373 (1.34%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 4 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 4 / 373 (1.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 2 / 192 (1.04%) | 4 / 373 (1.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic candida | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 373 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth infection | | | |

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported