



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients

Summary

| | |
|--------------------------|--|
| EudraCT number | 2015-004726-34 |
| Trial protocol | HU DE GB ES BE CZ PL FR HR IT GR AT Outside EU/EEA |
| Global end of trial date | 01 July 2022 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 04 January 2023 |
| First version publication date | 04 January 2023 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | SHP620-302 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02927067 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Shire |
| Sponsor organisation address | 300 Shire Way, Lexington, MA, United States, 02421 |
| Public contact | Study Director, Shire, ClinicalTransparency@shire.com |
| Scientific contact | Study Director, Shire, ClinicalTransparency@shire.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000353-PIP02-16 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 01 July 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 July 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to compare the efficacy of maribavir to valganciclovir in CMV viremia clearance at the end of Study Week 8 in asymptomatic CMV infection in Hematopoietic Stem Cell Transplant (HSCT) recipients.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 14 April 2017 |
| 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 | Australia: 32 |
| Country: Number of subjects enrolled | China: 18 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | New Zealand: 17 |
| Country: Number of subjects enrolled | Singapore: 18 |
| Country: Number of subjects enrolled | Belgium: 61 |
| Country: Number of subjects enrolled | Switzerland: 6 |
| Country: Number of subjects enrolled | Czechia: 2 |
| Country: Number of subjects enrolled | Germany: 20 |
| Country: Number of subjects enrolled | Spain: 130 |
| Country: Number of subjects enrolled | France: 48 |
| Country: Number of subjects enrolled | United Kingdom: 28 |
| Country: Number of subjects enrolled | Greece: 1 |
| Country: Number of subjects enrolled | Croatia: 8 |
| Country: Number of subjects enrolled | Hungary: 3 |
| Country: Number of subjects enrolled | Israel: 4 |
| Country: Number of subjects enrolled | Italy: 11 |
| Country: Number of subjects enrolled | Poland: 3 |
| Country: Number of subjects enrolled | Russian Federation: 1 |
| Country: Number of subjects enrolled | Turkey: 11 |
| Country: Number of subjects enrolled | Canada: 15 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 111 |
| Worldwide total number of subjects | 553 |
| EEA total number of subjects | 287 |

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) | 4 |
| Adults (18-64 years) | 421 |
| From 65 to 84 years | 128 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were randomized at 97 sites in United States, Spain, France, Germany, United Kingdom, Belgium, China, Italy, Israel, Australia, Canada, Singapore, Croatia, Czech Republic, Greece, Hungary, Korea, New Zealand, Poland, Russia, Switzerland, and Turkey from 14 April 2017 (first participant first visit) to 01 July 2022 (last participant last visit).

Pre-assignment

Screening details:

Participants who were hematopoietic stem cell transplant (HSCT) recipients with a diagnosis of asymptomatic cytomegalovirus (CMV) infection were enrolled then randomized in a 1:1 ratio to receive either maribavir or valganciclovir (along with placebo matched to comparator) in each arm in a double-blind, double-dummy fashion.

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 |

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Valganciclovir 900 mg BID |

Arm description:

Participants received 900 milligrams (mg) of valganciclovir along with a placebo matched to maribavir, twice daily (BID) orally for 8 weeks. Valganciclovir dose was allowed to be adjusted to 450 mg BID or 450 mg QD based on renal function impairment assessed at baseline or development of neutropenia during the study.

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

Dosage and administration details:

Placebo tablets matched to maribavir.

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

Dosage and administration details:

Valganciclovir 900 mg, BID. Dose was adjusted to 450 mg BID or 450 mg QD during the study for renal function impairment or neutropenia.

| | |
|------------------|----------------------|
| Arm title | Maribavir 400 mg BID |
|------------------|----------------------|

Arm description:

Participants received 400 mg of maribavir along with a placebo matched to valganciclovir, BID orally for 8 weeks.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Placebo tablets matched to valganciclovir. | |
| Investigational medicinal product name | Maribavir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Maribavir 400 mg BID. | |

| Number of subjects in period 1 | Valganciclovir 900 mg BID | Maribavir 400 mg BID |
|---|---------------------------|----------------------|
| Started | 277 | 276 |
| Treated Participants | 274 | 273 |
| Participants Received 8 Weeks Treatment | 140 ^[1] | 179 ^[2] |
| Completed | 217 | 215 |
| Not completed | 60 | 61 |
| Adverse event, serious fatal | 18 | 31 |
| Adverse event, non-fatal | 13 | 10 |
| Withdrawn Consent | 20 | 12 |
| Reason not Specified | 4 | 6 |
| Noncompliance | 5 | 2 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants who received 8 weeks of treatment include the participants who completed study drug treatment.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Treated participants (full analysis set) included the participants from the randomized set who took at least one dose of assigned study drug and were analyzed for efficacy and safety evaluations.

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Valganciclovir 900 mg BID |
|-----------------------|---------------------------|

Reporting group description:

Participants received 900 milligrams (mg) of valganciclovir along with a placebo matched to maribavir, twice daily (BID) orally for 8 weeks. Valganciclovir dose was allowed to be adjusted to 450 mg BID or 450 mg QD based on renal function impairment assessed at baseline or development of neutropenia during the study.

| | |
|-----------------------|----------------------|
| Reporting group title | Maribavir 400 mg BID |
|-----------------------|----------------------|

Reporting group description:

Participants received 400 mg of maribavir along with a placebo matched to valganciclovir, BID orally for 8 weeks.

| Reporting group values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | Total |
|------------------------------------|---------------------------|----------------------|-------|
| Number of subjects | 277 | 276 | 553 |
| Age Categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----------------|-----|
| Age continuous Units: years arithmetic mean standard deviation | 51.8 ± 15.22 | 53.1 ± 13.96 | - |
| Gender categorical Units: Subjects | | | |
| Female | 110 | 126 | 236 |
| Male | 167 | 150 | 317 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Asian | 39 | 36 | 75 |
| Native Hawaiian or Other Pacific Islander | 3 | 0 | 3 |
| Black or African American | 9 | 10 | 19 |
| White | 200 | 221 | 421 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 25 | 9 | 34 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 37 | 35 | 72 |
| Not Hispanic or Latino | 193 | 216 | 409 |
| Unknown or Not Reported | 47 | 25 | 72 |
| Region of Enrollment Units: Subjects | | | |
| Australia Australia | 13 | 19 | 32 |
| China China | 9 | 9 | 18 |
| Korea, South Korea, Republic of | 3 | 2 | 5 |
| New Zealand New Zealand | 10 | 7 | 17 |
| Belgium Belgium | 31 | 30 | 61 |
| Switzerland Switzerland | 4 | 2 | 6 |

| | | | |
|--|----------|----------|-----|
| Czech Republic Czechia | 0 | 2 | 2 |
| Germany Germany | 9 | 11 | 20 |
| Spain Spain | 61 | 69 | 130 |
| France France | 34 | 14 | 48 |
| United Kingdom United Kingdom | 14 | 14 | 28 |
| Greece Greece | 1 | 0 | 1 |
| Croatia Croatia | 4 | 4 | 8 |
| Hungary Hungary | 2 | 1 | 3 |
| Israel Israel | 2 | 2 | 4 |
| Italy Italy | 7 | 4 | 11 |
| Poland Poland | 1 | 2 | 3 |
| Russia Russia | 1 | 0 | 1 |
| Turkey Turkey | 6 | 5 | 11 |
| Canada Canada | 8 | 7 | 15 |
| United States United States | 50 | 61 | 111 |
| Singapore Singapore | 7 | 11 | 18 |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 169.58 | 168.75 | |
| standard deviation | ± 9.391 | ± 9.579 | - |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 70.31 | 70.98 | |
| standard deviation | ± 15.247 | ± 16.779 | - |
| Body Mass Index (BMI) | | | |
| BMI = Body Mass Index. It is computed by [weight (kg) / height (cm)^2] x 10,000. | | | |
| Units: kg/m^2 | | | |
| arithmetic mean | 24.38 | 24.90 | |
| standard deviation | ± 4.628 | ± 5.007 | - |

End points

End points reporting groups

| | |
|--|---------------------------|
| Reporting group title | Valganciclovir 900 mg BID |
| Reporting group description: Participants received 900 milligrams (mg) of valganciclovir along with a placebo matched to maribavir, twice daily (BID) orally for 8 weeks. Valganciclovir dose was allowed to be adjusted to 450 mg BID or 450 mg QD based on renal function impairment assessed at baseline or development of neutropenia during the study. | |
| Reporting group title | Maribavir 400 mg BID |
| Reporting group description: Participants received 400 mg of maribavir along with a placebo matched to valganciclovir, BID orally for 8 weeks. | |

Primary: Number of Participants Who Achieved Confirmed Clearance of Plasma Cytomegalovirus (CMV) Deoxyribose Nucleic Acid (DNA) at the end of Study Week 8

| | |
|---|---|
| End point title | Number of Participants Who Achieved Confirmed Clearance of Plasma Cytomegalovirus (CMV) Deoxyribose Nucleic Acid (DNA) at the end of Study Week 8 |
| End point description: Confirmed CMV viremia clearance is defined as plasma CMV DNA concentrations less than lower limit of quantification (LLOQ; i.e. <137 International units per milliliter [IU/mL]), when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive post baseline samples separated by at least 5 days. To be considered a responder for the primary endpoint, the participant must have received exclusively study-assigned treatment (regardless of whether study-assigned treatment was completed). | |
| End point type | Primary |
| End point timeframe: Week 8 | |

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 273 | | |
| Units: participants | 212 | 190 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Maribavir 400 mg BID v Valganciclovir 900 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | -7.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.98 |
| upper limit | -0.36 |

Notes:

[1] - The non-inferiority (NI) margin of the primary efficacy endpoint was 7%. If the lower limit of the 95% confidence interval (CI) was greater than -7%, then NI was assumed. Assuming 68% (maribavir) and 60% (valganciclovir) subjects achieve confirmed viremia clearance, 494 subjects (247 per group) will yield >90% power to declare NI based on 2-group test of equivalence in proportions (nQuery Advisor 7.0). Considering 10% dropout, 550 subjects (275 subjects per group) were enrolled and randomized.

Secondary: Number of Participants who Achieved Confirmed CMV Viremia Clearance and CMV Infection Symptom Control at the end of Week 8, Followed by Maintenance of Treatment Effect at Week 16

| | |
|-----------------|--|
| End point title | Number of Participants who Achieved Confirmed CMV Viremia Clearance and CMV Infection Symptom Control at the end of Week 8, Followed by Maintenance of Treatment Effect at Week 16 |
|-----------------|--|

End point description:

Confirmed CMV viremia clearance is defined as plasma CMV DNA concentrations less than lower limit of quantification (LLOQ; i.e. <137 International units per milliliter [IU/mL]), when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive post baseline samples separated by at least 5 days. To be considered a responder for this key secondary endpoint, the participant must have received exclusively study-assigned treatment (regardless of whether study-assigned treatment was completed).

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

End point timeframe:

Week 8 up to Week 16

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 273 | | |
| Units: participants | 133 | 144 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | 4.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.91 |
| upper limit | 12.76 |

Notes:

[2] - The non-inferiority margin of the key secondary efficacy endpoint was 7%. If the lower limit of the 95% CI was greater than -7%, then noninferiority (NI) was assumed. Because the NI of the primary efficacy endpoint was not established, the NI hypothesis of the key secondary endpoint was not tested formally.

Secondary: Number of Participants who Achieved Confirmed Clearance of Plasma CMV DNA (CMV Viremia Clearance) at Week 8 After Receiving 8 Weeks of Study Assigned Treatment

| | |
|-----------------|---|
| End point title | Number of Participants who Achieved Confirmed Clearance of Plasma CMV DNA (CMV Viremia Clearance) at Week 8 After Receiving 8 Weeks of Study Assigned Treatment |
|-----------------|---|

End point description:

Confirmed CMV viremia clearance is defined as plasma CMV DNA concentrations less than lower limit of quantification (LLOQ; i.e. <137 International units per milliliter [IU/mL]), when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive post baseline samples separated by at least 5 days. To be considered a responder for this secondary endpoint, the participant must have received exclusively study-assigned treatment for 8 weeks. Participants who discontinued treatment early were non-responders for this endpoint.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 8 | |

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 273 | | |
| Units: participants | 137 | 158 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.061 [3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | 8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | 16.3 |

Notes:

[3] - The CMH weighted average approach (stratified for baseline plasma CMV DNA concentration and acute GVHD status) was used for the adjusted difference in percentage of responders (Maribavir–Valganciclovir), the corresponding 95% CI, and the p–value.

Secondary: Number of Participants who Achieved Confirmed CMV Viremia Clearance

After Receiving 8 Weeks of Study-assigned Treatment Through Weeks 12, 16 and 20

| | |
|-----------------|---|
| End point title | Number of Participants who Achieved Confirmed CMV Viremia Clearance After Receiving 8 Weeks of Study-assigned Treatment Through Weeks 12, 16 and 20 |
|-----------------|---|

End point description:

Confirmed CMV viremia clearance is defined as plasma CMV DNA concentrations less than lower limit of quantification (LLOQ; i.e. <137 International units per milliliter [IU/mL]), when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive post baseline samples separated by at least 5 days. To be considered a responder for this secondary endpoint, the participant must have received exclusively study-assigned treatment for 8 weeks.

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

End point timeframe:

Week 8 through Weeks 12, 16 and 20

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 273 | | |
| Units: participants | | | | |
| Week 8 | 137 | 158 | | |
| Week 12 | 98 | 134 | | |
| Week 16 | 82 | 119 | | |
| Week 20 | 72 | 98 | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.061 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | 8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | 16.3 |

Notes:

[4] - The CMH weighted average approach (stratified for baseline plasma CMV DNA concentration and acute GVHD status) was used for the adjusted difference in percentage of responders (Maribavir–Valganciclovir), the corresponding 95% CI, and the p–value.

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Week 12

| | |
|---|--|
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[5] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | 13.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.23 |
| upper limit | 21.62 |

Notes:

[5] - The CMH weighted average approach (stratified for baseline plasma CMV DNA concentration and acute GVHD status) was used for the adjusted difference in percentage of responders (Maribavir–Valganciclovir), the corresponding 95% CI, and the p–value.

Statistical analysis title

Statistical Analysis 3

Statistical analysis description:

Week 16

| | |
|---|--|
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | 13.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.8 |
| upper limit | 21.87 |

Notes:

[6] - The CMH weighted average approach (stratified for baseline plasma CMV DNA concentration and acute GVHD status) was used for the adjusted difference in percentage of responders (Maribavir–Valganciclovir), the corresponding 95% CI, and the p–value.

Statistical analysis title

Statistical Analysis 4

Statistical analysis description:

Week 20

| | |
|---|--|
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.014 ^[7] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | 9.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.98 |
| upper limit | 17.5 |

Notes:

[7] - The CMH weighted average approach (stratified for baseline plasma CMV DNA concentration and acute GVHD status) was used for the adjusted difference in percentage of responders (Maribavir–Valganciclovir), the corresponding 95% CI, and the p–value.

Secondary: Number of Participants who Achieved Confirmed CMV Viremia Clearance and CMV Infection Symptom Control at Study Week 8 With Maintenance Through Weeks 12 and 20

| | |
|-----------------|--|
| End point title | Number of Participants who Achieved Confirmed CMV Viremia Clearance and CMV Infection Symptom Control at Study Week 8 With Maintenance Through Weeks 12 and 20 |
|-----------------|--|

End point description:

Confirmed CMV viremia clearance is defined as plasma CMV DNA concentrations less than lower limit of quantification (LLOQ; i.e. <137 International units per milliliter [IU/mL]), when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive post baseline samples separated by at least 5 days. To be considered a responder for this secondary endpoint, the participant must have received exclusively study-assigned treatment (regardless of whether study-assigned treatment was completed) and had no symptoms of tissue invasive CMV disease at Week 8, Week 8 through Week 12, and Week 8 through Week 20, respectively.

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

End point timeframe:

Week 8 through Weeks 12 and 20

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 273 | | |
| Units: participants | | | | |
| Week 8 | 211 | 190 | | |
| Week 12 | 157 | 162 | | |
| Week 20 | 116 | 118 | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.051 ^[8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | -7.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.64 |
| upper limit | 0.02 |

Notes:

[8] - The CMH weighted average approach (stratified for baseline plasma CMV DNA concentration and acute GVHD status) was used for the adjusted difference in percentage of responders (Maribavir–Valganciclovir), the corresponding 95% CI, and the p–value.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 20

| | |
|---|--|
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.809 ^[9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | 1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.27 |
| upper limit | 9.31 |

Notes:

[9] - The CMH weighted average approach (stratified for baseline plasma CMV DNA concentration and acute GVHD status) was used for the adjusted difference in percentage of responders (Maribavir–Valganciclovir), the corresponding 95% CI, and the p–value.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 12

| | |
|---|--|
| Comparison groups | Valganciclovir 900 mg BID v Maribavir 400 mg BID |
| Number of subjects included in analysis | 547 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.606 ^[10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentage of Responders |
| Point estimate | 2.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.05 |
| upper limit | 10.37 |

Notes:

[10] - The CMH weighted average approach (stratified for baseline plasma CMV DNA concentration and acute GVHD status) was used for the adjusted difference in percentage of responders (Maribavir–Valganciclovir), the corresponding 95% CI, and the p–value.

Secondary: Number of Participants With Confirmed Recurrence of Viremia During First 8 Weeks of the Study

| | |
|---|---|
| End point title | Number of Participants With Confirmed Recurrence of Viremia During First 8 Weeks of the Study |
| End point description: Recurrence of CMV viremia is defined as plasma CMV DNA concentration greater than or equal to (\geq) LLOQ when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive plasma samples at least 5 days apart, after being unquantifiable ($<$ LLOQ) for at least 5 days in 2 consecutive samples during the first 8 weeks of the study, during the 12 weeks of the follow up study phase, and at any time during the study. | |
| End point type | Secondary |
| End point timeframe: Up to Week 8 | |

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 236 | 226 | | |
| Units: participants | 6 | 16 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Confirmed Recurrence of Viremia During the Follow-up Period

| | |
|---|---|
| End point title | Number of Participants With Confirmed Recurrence of Viremia During the Follow-up Period |
| End point description: Recurrence of CMV viremia is defined as plasma CMV DNA concentration greater than or equal to (\geq) LLOQ when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive plasma samples at least 5 days apart, after being unquantifiable ($<$ LLOQ) for at least 5 days in 2 consecutive samples during the first 8 weeks of the study, during the 12 weeks of the follow up study phase, and at any time during the study. | |
| End point type | Secondary |
| End point timeframe: From Week 9 up to Week 20 | |

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 236 | 226 | | |
| Units: participants | 47 | 27 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Confirmed Recurrence of Viremia at any Time During the Study

| | |
|-----------------|--|
| End point title | Number of Participants With Confirmed Recurrence of Viremia at any Time During the Study |
|-----------------|--|

End point description:

Recurrence of CMV viremia is defined as plasma CMV DNA concentration greater than or equal to (\geq) LLOQ when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive plasma samples at least 5 days apart, after being unquantifiable ($<$ LLOQ) for at least 5 days in 2 consecutive samples during the first 8 weeks of the study, during the 12 weeks of the follow up study phase, and at any time during the study.

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

End point timeframe:

Up to Week 20

| | | | | |
|-----------------------------|------------------------------|-------------------------|--|--|
| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 236 | 226 | | |
| Units: participants | 53 | 43 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Confirmed Recurrence of Viremia While on Study Treatment and Off Treatment

| | |
|-----------------|--|
| End point title | Number of Participants With Confirmed Recurrence of Viremia While on Study Treatment and Off Treatment |
|-----------------|--|

End point description:

Recurrence of CMV viremia is defined as plasma CMV DNA concentration greater than or equal to (\geq) LLOQ when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive plasma samples at least 5 days apart, after being unquantifiable ($<$ LLOQ) for at least 5 days in 2 consecutive samples during the first 8 weeks of the study, during the 12 weeks of the follow up study phase, and at any time during the study.

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

End point timeframe:

Baseline up to Week 20

| | | | | |
|-----------------------------|------------------------------|-------------------------|--|--|
| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 236 | 226 | | |
| Units: participants | | | | |
| On Study | 0 | 14 | | |
| Off Study | 53 | 29 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Grade 3 or 4 (Shift from Baseline Grade <3) and Grade 4 Neutropenia (Shift from Baseline Grade <4) While on Study Treatment

| | |
|-----------------|--|
| End point title | Incidence of Grade 3 or 4 (Shift from Baseline Grade <3) and Grade 4 Neutropenia (Shift from Baseline Grade <4) While on Study Treatment |
|-----------------|--|

End point description:

Grade 3 and grade 4 neutropenia are defined as absolute neutrophil count (ANC) <1000 per cubic millimeter (/mm³) and ANC <500/mm³ respectively. Incidence of Grade 3 or 4 neutropenia represents the percentage of participants with Grade <3 (or missing) neutropenia at baseline, but Grade 3 or 4 while on study treatment. Incidence of Grade 4 neutropenia represents the number of participants with Grade <4 (or missing) neutropenia at baseline, but Grade 4 while on study treatment.

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

End point timeframe:

From start of study drug to end of study drug + 1 day (up to approximately Week 8)

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|--------------------------------|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 273 | | |
| Units: participants | | | | |
| Grade 3 or Grade 4 Neutropenia | 137 | 44 | | |
| Grade 4 Neutropenia | 61 | 9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events During the on-Treatment Period

| | |
|-----------------|--|
| End point title | Number of Participants With Treatment-Emergent Adverse Events During the on-Treatment Period |
|-----------------|--|

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical investigation participants administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE that has a start date on or after the first dose of study treatment, or that has a start date before the date of first dose of study treatment but increases in severity after the first dose of study treatment, will be considered a treatment-emergent AE (TEAE).

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

End point timeframe:

From the start of the study treatment to 7 days after the last dose of study treatment (up to

| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
|-----------------------------|------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 273 | | |
| Units: participants | 269 | 268 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Concentration (Cmin) of Maribavir

| | |
|-----------------|---|
| End point title | Predose Concentration (Cmin) of Maribavir ^[11] |
|-----------------|---|

End point description:

The primary plasma maribavir concentration dataset (primary concentration dataset) includes all plasma maribavir concentrations. Missing PK sampling times are imputed according to the sparse sampling schedule in primary concentration dataset.

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

End point timeframe:

Weeks 1, 4, and 8: pre-morning dose

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint.

| End point values | Maribavir 400 mg BID | | | |
|--|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 225 | | | |
| Units: micrograms per milliliter (µg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8 (n=225) | 9.17 (± 7.69) | | | |
| Week 4 (n=190) | 8.71 (± 9.20) | | | |
| Week 8 (n=164) | 7.02 (± 6.35) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve Over the 12-Hour Dosing Interval at Steady State AUC(0-tau) of Maribavir for Adolescent Participants Only

| | |
|-----------------|---|
| End point title | Area Under the Concentration-Time Curve Over the 12-Hour Dosing Interval at Steady State AUC(0-tau) of Maribavir for Adolescent Participants Only ^[12] |
|-----------------|---|

End point description:

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

End point timeframe:

Pre-morning dose, 1, 2, 3, 4, 6, 8, and 12 hours post-morning dose of Week 1

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint.

| | | | | |
|--|----------------------|--|--|--|
| End point values | Maribavir 400 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: hours (h)*µg/mL | | | | |
| arithmetic mean (full range (min-max)) | 161 (161 to 161) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Maribavir for Adolescent Participants Only

| | |
|-----------------|--|
| End point title | Maximum Observed Plasma Concentration (Cmax) of Maribavir for Adolescent Participants Only ^[13] |
|-----------------|--|

End point description:

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

End point timeframe:

Pre-morning dose, 1, 2, 3, 4, 6, 8, and 12 hours post-morning dose of Week 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint.

| | | | | |
|--|----------------------|--|--|--|
| End point values | Maribavir 400 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: µg/mL | | | | |
| arithmetic mean (full range (min-max)) | 22.0 (22.0 to 22.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time When Maximum Concentration is Observed (Tmax) of Maribavir for Adolescent Participants Only

| | |
|-----------------|--|
| End point title | Time When Maximum Concentration is Observed (Tmax) of Maribavir for Adolescent Participants Only ^[14] |
|-----------------|--|

End point description:

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

End point timeframe:

Pre-morning dose, 1, 2, 3, 4, 6, 8, and 12 hours post-morning dose of Week 1

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint.

| | | | | |
|-------------------------------|----------------------|--|--|--|
| End point values | Maribavir 400 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: hours (h) | | | | |
| median (full range (min-max)) | 0.92 (0.92 to 0.92) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Oral Clearance (CL/F) of Maribavir for Adolescent Participants Only

| | |
|-----------------|--|
| End point title | Apparent Oral Clearance (CL/F) of Maribavir for Adolescent Participants Only ^[15] |
|-----------------|--|

End point description:

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

End point timeframe:

Pre-morning dose, 1, 2, 3, 4, 6, 8, and 12 hours post-morning dose of Week 1

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint.

| | | | | |
|--|----------------------|--|--|--|
| End point values | Maribavir 400 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: liters per hour (L/h) | | | | |
| arithmetic mean (full range (min-max)) | 2.49 (2.49 to 2.49) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (V_z/F) of Maribavir for Adolescent Participants Only

| | |
|-----------------|---|
| End point title | Apparent Volume of Distribution (V _z /F) of Maribavir for Adolescent Participants Only ^[16] |
|-----------------|---|

End point description:

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

End point timeframe:

Pre-morning dose, 1, 2, 3, 4, 6, 8, and 12 hours post-morning dose of Week 1

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint.

| | | | | |
|--|----------------------|--|--|--|
| End point values | Maribavir 400 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: liters (L) | | | | |
| arithmetic mean (full range (min-max)) | 18.3 (18.3 to 18.3) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants Developing Resistance

| | |
|-----------------|--|
| End point title | Percentage of Participants Developing Resistance |
|-----------------|--|

End point description:

Resistance development was low in the two treatment arms and numerically higher in the maribavir arm. Percentages are rounded to one decimal place.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From start of study drug up to end of the study (up to Week 20)

| | | | | |
|-----------------------------------|---------------------------|----------------------|--|--|
| End point values | Valganciclovir 900 mg BID | Maribavir 400 mg BID | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 274 | 273 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 2.9 | 8.8 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: From start of study drug up to end of the study (up to Week 20); Serious and Other Adverse Events: From the start of the study drug to 7 days after the last dose of study treatment (up to approximately Week 9)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Maribavir 400 mg BID |
|-----------------------|----------------------|

Reporting group description:

Participants received 400 mg of maribavir along with a placebo matched to valganciclovir, BID orally for 8 weeks.

| | |
|-----------------------|---------------------------|
| Reporting group title | Valganciclovir 900 mg BID |
|-----------------------|---------------------------|

Reporting group description:

Participants received 900 mg of valganciclovir along with a placebo matched to maribavir, twice daily (BID) orally for 8 weeks. Valganciclovir dose was allowed to be adjusted to 450 mg BID or 450 mg QD based on renal function impairment assessed at baseline or development of neutropenia during the study.

| Serious adverse events | Maribavir 400 mg BID | Valganciclovir 900 mg BID | |
|---|----------------------|---------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 88 / 273 (32.23%) | 95 / 274 (34.67%) | |
| number of deaths (all causes) | 37 | 29 | |
| number of deaths resulting from adverse events | 18 | 12 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia recurrent | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 2 / 274 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute myeloid leukaemia recurrent | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 273 (0.73%) | 2 / 274 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| B precursor type acute leukaemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Leukaemic infiltration | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lymphoma | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Non-Hodgkin's lymphoma recurrent | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transformation to acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 2 / 273 (0.73%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 273 (2.93%) | 13 / 274 (4.74%) | |
| occurrences causally related to treatment / all | 0 / 9 | 1 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Acute graft versus host disease in skin | | | |
| subjects affected / exposed | 4 / 273 (1.47%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|-----------------|--|
| Acute graft versus host disease in intestine | | | |
| subjects affected / exposed | 10 / 273 (3.66%) | 4 / 274 (1.46%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 0 | |
| Chronic graft versus host disease | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute graft versus host disease oral | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic graft versus host disease in eye | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic graft versus host disease in intestine | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemophagocytic lymphohistiocytosis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transplant rejection | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Vulvovaginal pruritus | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (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 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cough | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 273 (1.10%) | 2 / 274 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hepatic enzyme increased subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product use issue | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Acute polyneuropathy | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autonomic nervous system imbalance | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system lesion | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limbic encephalitis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 3 / 274 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nystagmus | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 273 (1.10%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 8 / 274 (2.92%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 3 / 274 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolysis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 3 / 274 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 4 / 273 (1.47%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Warm type haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Neurosensory hypoacusis | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 273 (1.47%) | 6 / 274 (2.19%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysbiosis | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 273 (0.73%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 5 / 274 (1.82%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------------------------|-----------------------------------|--|
| Infections and infestations Bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 273 (0.37%) 0 / 1 0 / 0 | 0 / 274 (0.00%) 0 / 0 0 / 0 | |
| Cystitis viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 273 (0.00%) 0 / 0 0 / 0 | 1 / 274 (0.36%) 0 / 1 0 / 0 | |
| COVID-19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 273 (0.00%) 0 / 0 0 / 0 | 1 / 274 (0.36%) 0 / 1 0 / 0 | |
| Cytomegalovirus colitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 273 (0.73%) 0 / 2 0 / 1 | 1 / 274 (0.36%) 0 / 1 0 / 0 | |
| Cytomegalovirus enterocolitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 273 (0.00%) 0 / 0 0 / 0 | 1 / 274 (0.36%) 0 / 1 0 / 0 | |
| Cytomegalovirus gastritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 273 (0.00%) 0 / 0 0 / 0 | 1 / 274 (0.36%) 0 / 1 0 / 0 | |
| Cytomegalovirus gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 273 (0.00%) 0 / 0 0 / 0 | 1 / 274 (0.36%) 0 / 1 0 / 0 | |
| Cytomegalovirus gastrointestinal infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 273 (0.37%) 0 / 1 0 / 0 | 0 / 274 (0.00%) 0 / 0 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 3 / 273 (1.10%) | 3 / 274 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus infection reactivation | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus oesophagitis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus viraemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 4 / 274 (1.46%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated toxoplasmosis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Epstein-Barr viraemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epstein-Barr virus infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 273 (0.73%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Eye infection toxoplasmal | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fournier's gangrene | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal sepsis | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis astroviral | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster disseminated | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster meningoencephalitis | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster reactivation | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection fungal | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nasopharyngitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| 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 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 273 (1.10%) | 3 / 274 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 2 / 274 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia parainfluenzae viral | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 2 / 274 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 2 / 274 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 273 (1.10%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 273 (0.00%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxoplasmosis | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella zoster virus infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 2 / 273 (0.73%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (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 | | | |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food intolerance | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 0 / 274 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 273 (0.37%) | 1 / 274 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 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 | Maribavir 400 mg BID | Valganciclovir 900 mg BID | |
|--|---------------------------------|--------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 245 / 273 (89.74%) | 256 / 274 (93.43%) | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 18 / 273 (6.59%) | 12 / 274 (4.38%) | |
| occurrences (all) | 18 | 13 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 13 / 273 (4.76%) | 29 / 274 (10.58%) | |
| occurrences (all) | 28 | 52 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 3 / 273 (1.10%) | 14 / 274 (5.11%) | |
| occurrences (all) | 4 | 15 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 17 / 273 (6.23%) | 16 / 274 (5.84%) | |
| occurrences (all) | 21 | 19 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 14 / 273 (5.13%) | 17 / 274 (6.20%) | |
| occurrences (all) | 15 | 19 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 30 / 273 (10.99%) | 14 / 274 (5.11%) | |
| occurrences (all) | 31 | 16 | |
| Dysgeusia | | | |
| subjects affected / exposed | 47 / 273 (17.22%) | 16 / 274 (5.84%) | |
| occurrences (all) | 51 | 17 | |
| Taste disorder | | | |
| subjects affected / exposed | 23 / 273 (8.42%) | 6 / 274 (2.19%) | |
| occurrences (all) | 24 | 6 | |
| Tremor | | | |
| subjects affected / exposed | 10 / 273 (3.66%) | 15 / 274 (5.47%) | |
| occurrences (all) | 13 | 16 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 273 (2.56%) | 27 / 274 (9.85%) | |
| occurrences (all) | 10 | 37 | |

| | | | |
|--|-------------------------|---------------------------|--|
| Anaemia subjects affected / exposed occurrences (all) | 62 / 273 (22.71%) 89 | 49 / 274 (17.88%) 57 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 31 / 273 (11.36%) 32 | 62 / 274 (22.63%) 79 | |
| Neutropenia subjects affected / exposed occurrences (all) | 44 / 273 (16.12%) 60 | 144 / 274 (52.55%) 247 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 13 / 273 (4.76%) 14 | 19 / 274 (6.93%) 22 | |
| Fatigue subjects affected / exposed occurrences (all) | 13 / 273 (4.76%) 13 | 19 / 274 (6.93%) 20 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 27 / 273 (9.89%) 29 | 26 / 274 (9.49%) 27 | |
| Pyrexia subjects affected / exposed occurrences (all) | 24 / 273 (8.79%) 29 | 25 / 274 (9.12%) 29 | |
| Immune system disorders | | | |
| Acute graft versus host disease in skin subjects affected / exposed occurrences (all) | 46 / 273 (16.85%) 55 | 32 / 274 (11.68%) 35 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 14 / 273 (5.13%) 16 | 19 / 274 (6.93%) 22 | |
| Constipation subjects affected / exposed occurrences (all) | 16 / 273 (5.86%) 17 | 10 / 274 (3.65%) 11 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 50 / 273 (18.32%) 67 | 44 / 274 (16.06%) 55 | |

| | | | |
|--|-------------------------|-------------------------|--|
| Nausea subjects affected / exposed occurrences (all) | 74 / 273 (27.11%) 89 | 64 / 274 (23.36%) 79 | |
| Vomiting subjects affected / exposed occurrences (all) | 55 / 273 (20.15%) 70 | 47 / 274 (17.15%) 59 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 20 / 273 (7.33%) 20 | 26 / 274 (9.49%) 28 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 2 / 273 (0.73%) 2 | 14 / 274 (5.11%) 16 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 10 / 273 (3.66%) 10 | 17 / 274 (6.20%) 19 | |
| Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all) | 24 / 273 (8.79%) 27 | 15 / 274 (5.47%) 19 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 18 / 273 (6.59%) 19 | 16 / 274 (5.84%) 16 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 23 / 273 (8.42%) 28 | 22 / 274 (8.03%) 23 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 01 March 2017 | -Modification of primary, key secondary, and secondary objectives to include participants who discontinue study treatment early and meet the criteria of confirmed CMV viremia clearance as responders in the primary efficacy analysis. - Modified Inclusion Criterion 5 to indicate that the current CMV infection must be the first episode of CMV viremia after HSCT, either primary or reactivation. - Clarified Inclusion Criterion 8 to indicate that urine pregnancy tests may be done per institutional requirements in addition to serum; however, they are not sufficient for eligibility determination. -Added a new Exclusion Criterion 3 to exclude participants with recurrent CMV infection. -Amended Exclusion Criterion 6 to indicate that participants must not be on treatment with anti-CMV agents (ganciclovir, valganciclovir, foscarnet or cidofovir) for the current CMV infection for longer than 72 hours. -Clarified in Exclusion Criterion 13 that subjects who have received an unapproved agent or device within 30 days before initiation of study treatment were not eligible. -Clarified Exclusion Criterion 16 indicating that known (previously documented) HIV historical results were accepted and no additional study testing was required. -Added an intensive PK sampling schedule for adolescents. -An additional pregnancy test at 4 weeks (Visit 6/Week 4) to obtain a monthly testing interval. -Addition of highly effective method of female and male contraception per the recommendations related to contraception and pregnancy testing in clinical trials by clinical trial facilitation group. -Addition recommendation for careful monitoring of concentration levels of concomitant medications that are substrates of CYP2C19 and P-gp both after initiation of maribavir (when substrate levels may increase) and after discontinuation of maribavir (when substrate levels may decrease), in alignment with the guidance to the investigators provided in the maribavir investigator's brochure. |
| 01 June 2017 | - Added "CMV CNS infection" as one of the reasons for discontinuation and/or withdrawal. -Added basic descriptive statistics generally for all endpoints. -Added sensitivity analysis for investigation of homogeneity of treatment effect across centers/regions. -Added rules for conducting the interim population PK analysis. |
| 01 September 2017 | -Revised storage conditions of investigational product. |
| 04 February 2019 | -Expanded eligibility criteria for viral load and creatinine clearance (CrCl). -Added a third viral-load stratum for participants with very low viral load and high-risk infection, in addition to the existing low viral-load and high viral-load strata. - Added a study visit at Study Day 4 (± 1) for participants taking a narrow therapeutic index immunosuppressive agent at baseline. -Added a visit 4 days after starting new therapy with a narrow therapeutic index immunosuppressive agent for participants who begin new therapy during the course of the treatment period to align the protocol with a recent recommendation from the DMC for Study SHP620-303. -Updated contact list, including removal of contacts for sites in Latin America. -Updated safety reporting contacts to a single Global Safety e-mail and fax contact per revised safety reporting procedures. -Added exclusion for concomitant letermovir and specified required washout period. -Clarified end of period for collecting nonserious AEs as up to 30 days after the last dose of study medication. -Modified the definition of overall study AEs to include events during the overall study period through the end of study, regardless of initiation of alternative anti-CMV treatment. -Modified criteria for reporting of CMV as an AE or SAE to harmonize with the reporting format used in Study SHP620-303. -Updated Table 12 Assessments of Responders for Key Secondary Endpoint (confirmed CMV viremia clearance at the end of Study Week 8 through Week 16) to ensure assessment of responder rates consistent with assessment specified in Study SHP620-303. -Eliminated the Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) assessment and deleted Appendix 5 containing the index. -Clarified language regarding starting dosage regimens, as updated entry criteria require expansion of starting doses. -Added Graft Versus Host Disease (GVHD) assessment criteria forms and added tables for GVHD diagnosis criteria. |

| | |
|-------------------|--|
| 11 February 2020 | -Added Modified Randomized Set, consisting of all participants in Randomized Set who take at least 1 dose of assigned study treatment. -Revised the exploratory efficacy endpoint of duration between the first confirmed CMV viremia clearance to viremia recurrence in all participants within 8 weeks of the study and through the end of study to time from the CMV viremia clearance at Week 8 to CMV viremia recurrence requiring alternative treatment. -Updated comorbidity status evaluation. -To align with the investigator's brochure, updated the Cmax and AUC values for the increased tacrolimus when concomitantly administered with maribavir and changed 2D6 substrate to CYP2C19 substrate. -Updated number of completed for Phase 1 studies. -Removed references to an electronic diary (e-diary) due to the introduction of paper back-up diaries. -Updated the versions of the Valcyte Prescribing Information and Summary of Product Characteristics (SmPC) to specify the current version as documented in the Study Pharmacy Manual. -Corrected the unit of measure for hemoglobin. -Clarified that timing of comorbidity status evaluation is at Visit 6/Week 4 and Visit 10/Week 8. -Clarified follow-up to closure of unresolved SAEs rather than AEs at end of study. -Corrected pregnancy reporting information to indicate that it is the investigator's responsibility to obtain pregnancy outcome/infant condition information within approximately 30 calendar days and 1 year postpartum. Removed requirement for a copy of the Investigational and Marketed Products Pregnancy Report Form being sent to the CRO/ sponsor medical monitor using details specified in the emergency contact information section of protocol. -Corrected information regarding reporting of SAEs. -Removed CIs from 3 secondary efficacy endpoints as they are not clinically meaningful for these analyses. |
| 06 December 2020 | -The protocol was amended to maintain participants safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by the COVID-19 pandemic. Amendment 6 provided flexibility to subjects to opt for home healthcare solutions as permitted by local regulations. This "hybrid study design" would offer subjects the option of in clinic or home healthcare for all study visits in the treatment phase. -Guidance was provided regarding changes to the study procedures that could be implemented for subjects or study sites affected by the COVID 19 Public Health Emergency. The guidance took references from the Food and Drug Administration Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 03 June 2020, and the European Medicines Agency (EMA) Guidance on the Management of Clinical Trials During the COVID 19 (Coronavirus) Pandemic, Version 3 (28 Apr 2020). |
| 24 March 2021 | -Removed language extending measures to other situations beyond the COVID-19 pandemic ("or other future similar unexpected public health concerns" as this section applies only to the current COVID 19 pandemic. -Updated the guidance on management of clinical trials during the COVID 19 pandemic. Clarified that the site must contact the sponsor for approval of the alternative method for obtaining informed consent prior to implementation. -Clarified the recording of abuse, misuse, overdose, and medication errors on the AE CRF. |
| 02 July 2021 | The main purpose of Amendment 8 was to update the sponsor name and address from Shire ViroPharma, Inc (Shire) to Takeda Development Center Americas, Inc (TDC Americas; Takeda) and to clarify the secondary endpoints. |
| 15 September 2021 | The main purpose of Amendment 9 was to update description of drug interactions consistent with the latest Investigator's Brochure. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported