



## Clinical trial results: Safety and Pharmacokinetics of Valganciclovir Syrup Formulation in Paediatric Solid Organ Transplant Recipients Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2004-000231-29 |
| Trial protocol           | ES GB          |
| Global end of trial date | 13 May 2005    |

### Results information

|                                |                                                                                                                           |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                              |
| This version publication date  | 18 November 2016                                                                                                          |
| First version publication date | 30 June 2016                                                                                                              |
| Version creation reason        | <ul style="list-style-type: none"><li>• New data added to full data set</li></ul> Update to record for alignment with CTg |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | WV16726 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00090766 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                                 |
|------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche AG                                                                                         |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070                                                              |
| Public contact               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG,<br>+41 61 6878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG,<br>+41 61 6878333, global.trial_information@roche.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 30 November 2007 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 13 May 2005      |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

1. To describe the safety and tolerability profile of valganciclovir powder for oral solution and tablets in pediatric solid organ transplant recipients
2. To determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir powder for oral solution and tablets in pediatric solid organ transplant recipients
3. To describe the incidence of cytomegalovirus (CMV) disease

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the declaration of Helsinki and the ICH E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all participants and/or their legally authorized representative. Participants signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug. Also, the independent Data Safety Monitoring Board ensured that participants were not put at undue risk.

Background therapy:

NA

Evidence for comparator:

Non-comparator study

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 28 May 2004 |
| Long term follow-up planned                               | Yes         |
| Long term follow-up rationale                             | Safety      |
| Long term follow-up duration                              | 3 Months    |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 18 |
| Country: Number of subjects enrolled | Australia: 6      |
| Country: Number of subjects enrolled | Canada: 9         |
| Country: Number of subjects enrolled | Mexico: 9         |
| Country: Number of subjects enrolled | Germany: 3        |
| Country: Number of subjects enrolled | France: 6         |
| Country: Number of subjects enrolled | Spain: 12         |
| Worldwide total number of subjects   | 63                |
| EEA total number of subjects         | 21                |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 13 |
| Children (2-11 years)                     | 25 |
| Adolescents (12-17 years)                 | 25 |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 63 participants were enrolled in this study conducted from 28 May 2004 to 13 May 2005. The study was conducted at 18 centers in 7 countries.

### Pre-assignment

Screening details:

Participants were screened within 48 hours prior to transplant surgery (Day 1) and received valganciclovir from Day 1.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|                              |                                         |
|------------------------------|-----------------------------------------|
| Are arms mutually exclusive? | Yes                                     |
| <b>Arm title</b>             | Valganciclovir age group $\leq 2$ years |

Arm description:

Eligible participants aged  $\leq 2$  years received valganciclovir up to maximum of 900 milligrams (mg) once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm ( $7 \times$  body surface area [BSA]  $\times$  creatinine clearance [CrCLS]).

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | Valganciclovir           |
| Investigational medicinal product code | RO 107 9070              |
| Other name                             | Valcyte                  |
| Pharmaceutical forms                   | Powder for oral solution |
| Routes of administration               | Oral use                 |

Dosage and administration details:

Valganciclovir powder was reconstituted with 91 millilitre (mL) of water to give a concentration of 50 mg/mL. Valganciclovir was also administered as a 450 mg film coated tablet if the projected dose was between 400 mg and 500 mg. If the projected dose was greater than 800 mg, two 450 mg tablets were taken. Valganciclovir powder for oral solution and/or tablets was administered to all the participants throughout 100 days dosing period.

|                  |                                               |
|------------------|-----------------------------------------------|
| <b>Arm title</b> | Valganciclovir age group $>2$ to $< 12$ years |
|------------------|-----------------------------------------------|

Arm description:

Eligible participants aged  $>2$  to  $< 12$  years received valganciclovir up to maximum of 900 mg once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm ( $7 \times$  BSA  $\times$  CrCLS).

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | Valganciclovir           |
| Investigational medicinal product code | RO 107 9070              |
| Other name                             | Valcyte                  |
| Pharmaceutical forms                   | Powder for oral solution |
| Routes of administration               | Oral use                 |

Dosage and administration details:

Valganciclovir powder was reconstituted with 91 mL of water to give a concentration of 50 mg/mL. Valganciclovir was also administered as a 450 mg film coated tablet if the projected dose was between 400 mg and 500 mg. If the projected dose was greater than 800 mg, two 450 mg tablets were taken. Valganciclovir powder for oral solution and/or tablets was administered to all the participants throughout 100 days dosing period.

|                  |                                          |
|------------------|------------------------------------------|
| <b>Arm title</b> | Valganciclovir age group $\geq 12$ years |
|------------------|------------------------------------------|

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**Arm description:**

Eligible participants aged  $\geq 12$  years received valganciclovir up to maximum of 900 mg once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm ( $7 * BSA * CrCL$ S).

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | Valganciclovir           |
| Investigational medicinal product code | RO 107 9070              |
| Other name                             | Valcyte                  |
| Pharmaceutical forms                   | Powder for oral solution |
| Routes of administration               | Oral use                 |

**Dosage and administration details:**

Valganciclovir powder was reconstituted with 91 mL of water to give a concentration of 50 mg/mL. Valganciclovir was also administered as a 450 mg film coated tablet if the projected dose was between 400 mg and 500 mg. If the projected dose was greater than 800 mg, two 450 mg tablets were taken. Valganciclovir powder for oral solution and/or tablets was administered to all the participants throughout 100 days dosing period.

| Number of subjects in period 1 | Valganciclovir age group $\leq 2$ years | Valganciclovir age group $>2$ to $< 12$ years | Valganciclovir age group $\geq 12$ years |
|--------------------------------|-----------------------------------------|-----------------------------------------------|------------------------------------------|
|                                |                                         |                                               |                                          |
| Started                        | 17                                      | 21                                            | 25                                       |
| Completed                      | 14                                      | 19                                            | 22                                       |
| Not completed                  | 3                                       | 2                                             | 3                                        |
| Nephrectomy Planned            | -                                       | -                                             | 1                                        |
| Death                          | 1                                       | -                                             | -                                        |
| Admin                          | -                                       | 2                                             | -                                        |
| Lost to follow-up              | 2                                       | -                                             | 2                                        |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                |                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                          | Valganciclovir age group ≤ 2 years        |
| Reporting group description:<br>Eligible participants aged ≤ 2 years received valganciclovir up to maximum of 900 milligrams (mg) once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm (7 * body surface area [BSA] * creatinine clearance [CrCLS]). |                                           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                          | Valganciclovir age group >2 to < 12 years |
| Reporting group description:<br>Eligible participants aged >2 to < 12 years received valganciclovir up to maximum of 900 mg once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm (7 * BSA * CrCLS).                                                  |                                           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                          | Valganciclovir age group ≥ 12 years       |
| Reporting group description:<br>Eligible participants aged ≥ 12 years received valganciclovir up to maximum of 900 mg once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm (7 * BSA * CrCLS).                                                        |                                           |

| Reporting group values                                                                                                                                                                                                                                    | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|-------------------------------------------|-------------------------------------|
| Number of subjects                                                                                                                                                                                                                                        | 17                                 | 21                                        | 25                                  |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                                    |                                           |                                     |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                    |                                           |                                     |
| Age continuous<br>Units: years                                                                                                                                                                                                                            |                                    |                                           |                                     |
| arithmetic mean                                                                                                                                                                                                                                           | 0.6                                | 6.9                                       | 14.2                                |
| standard deviation                                                                                                                                                                                                                                        | ± 0.86                             | ± 3.15                                    | ± 1.54                              |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                     |                                    |                                           |                                     |
| Female                                                                                                                                                                                                                                                    | 9                                  | 7                                         | 13                                  |
| Male                                                                                                                                                                                                                                                      | 8                                  | 14                                        | 12                                  |

| Reporting group values                                         | Total  |  |  |
|----------------------------------------------------------------|--------|--|--|
| Number of subjects                                             | 63     |  |  |
| Age categorical<br>Units: Subjects                             |        |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks) | 0<br>0 |  |  |

|                                          |    |  |  |
|------------------------------------------|----|--|--|
| Newborns (0-27 days)                     | 0  |  |  |
| Infants and toddlers (28 days-23 months) | 0  |  |  |
| Children (2-11 years)                    | 0  |  |  |
| Adolescents (12-17 years)                | 0  |  |  |
| Adults (18-64 years)                     | 0  |  |  |
| From 65-84 years                         | 0  |  |  |
| 85 years and over                        | 0  |  |  |
| Age continuous                           |    |  |  |
| Units: years                             |    |  |  |
| arithmetic mean                          |    |  |  |
| standard deviation                       | -  |  |  |
| Gender categorical                       |    |  |  |
| Units: Subjects                          |    |  |  |
| Female                                   | 29 |  |  |
| Male                                     | 34 |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                |                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                          | Valganciclovir age group ≤ 2 years        |
| Reporting group description:<br>Eligible participants aged ≤ 2 years received valganciclovir up to maximum of 900 milligrams (mg) once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm (7 * body surface area [BSA] * creatinine clearance [CrCLS]). |                                           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                          | Valganciclovir age group >2 to < 12 years |
| Reporting group description:<br>Eligible participants aged >2 to < 12 years received valganciclovir up to maximum of 900 mg once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm (7 * BSA * CrCLS).                                                  |                                           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                          | Valganciclovir age group ≥ 12 years       |
| Reporting group description:<br>Eligible participants aged ≥ 12 years received valganciclovir up to maximum of 900 mg once daily oral dose (solution or tablets) from the time of kidney transplantation for up to 100 days post-transplant. Dose was calculated using the algorithm (7 * BSA * CrCLS).                                                        |                                           |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                     | Safety population                         |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                      | Safety analysis                           |
| Subject analysis set description:<br>All participants who received at least one dose of valganciclovir were included in the safety analysis.                                                                                                                                                                                                                   |                                           |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                     | ITT population                            |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                      | Intention-to-treat                        |
| Subject analysis set description:<br>The ITT population comprised all participants who received at least one dose of the study drug, whether on-study or prematurely withdrawn.                                                                                                                                                                                |                                           |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                     | PK population                             |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                      | Sub-group analysis                        |
| Subject analysis set description:<br>The population PK analysis comprised all participants from studies WP16296, WP16303 and WV16726 who completed the specified treatment and from whom at least one plasma sample was taken.                                                                                                                                 |                                           |

### Primary: Number of Participants with Adverse Events Leading to Dose Interruption or Modification

|                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                  | Number of Participants with Adverse Events Leading to Dose Interruption or Modification <sup>[1]</sup> |
| End point description:<br>An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation in participant administered a pharmaceutical product, which did not necessarily have to have a causal relationship with this treatment. The number of participants with AEs leading to dose interruptions or modifications are reported. Safety population was used for the analysis. |                                                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                   | Primary                                                                                                |
| End point timeframe:<br>Up to Week 26                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                        |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this outcome measure



| End point values            | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |  |
|-----------------------------|------------------------------------|-------------------------------------------|-------------------------------------|--|
| Subject group type          | Reporting group                    | Reporting group                           | Reporting group                     |  |
| Number of subjects analysed | 17                                 | 21                                        | 25                                  |  |
| Units: Participants         | 4                                  | 2                                         | 3                                   |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Opportunistic Infections

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Number of Participants with Opportunistic Infections <sup>[2]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

Opportunistic infections included oral candidiasis, candidiasis, herpes simplex, cytomegalovirus antigen positive, cytomegalovirus test positive. The number of participants with opportunistic infections are reported. Safety population was used for the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to Week 26

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this outcome measure

| End point values                 | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |  |
|----------------------------------|------------------------------------|-------------------------------------------|-------------------------------------|--|
| Subject group type               | Reporting group                    | Reporting group                           | Reporting group                     |  |
| Number of subjects analysed      | 17                                 | 21                                        | 25                                  |  |
| Units: Participants              |                                    |                                           |                                     |  |
| Oral Candidiasis                 | 2                                  | 0                                         | 0                                   |  |
| Candidiasis                      | 1                                  | 0                                         | 0                                   |  |
| Herpes Simplex                   | 0                                  | 1                                         | 0                                   |  |
| Cytomegalovirus Antigen Positive | 1                                  | 0                                         | 0                                   |  |
| Cytomegalovirus Test Positive    | 1                                  | 0                                         | 0                                   |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Any Adverse Events and Any Serious Adverse Events

|                 |                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Any Adverse Events and Any Serious Adverse Events <sup>[3]</sup> |
|-----------------|----------------------------------------------------------------------------------------------|

End point description:

An AE was defined as any untoward medical occurrence in a participant or clinical investigation in participant administered a pharmaceutical product, which did not necessarily have to have a causal relationship with this treatment. A serious adverse event (SAE) is any experience or a significant hazard, that is fatal, life-threatening, requires in-patient hospitalization or prolongation of existing one, results in

persistent or significant disability, is a congenital anomaly, is medically significant or requires intervention to prevent one or other of the outcomes listed above. Safety population was used for the analysis.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Up to Week 26        |         |

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this outcome measure

| End point values            | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |  |
|-----------------------------|------------------------------------|-------------------------------------------|-------------------------------------|--|
| Subject group type          | Reporting group                    | Reporting group                           | Reporting group                     |  |
| Number of subjects analysed | 17                                 | 21                                        | 25                                  |  |
| Units: Participants         |                                    |                                           |                                     |  |
| Any AE                      | 17                                 | 18                                        | 24                                  |  |
| Any SAE                     | 13                                 | 11                                        | 11                                  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Mean Area Under the Concentration-Time Curve From 0 to 24 Hours of Valganciclovir

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Mean Area Under the Concentration-Time Curve From 0 to 24 Hours of Valganciclovir <sup>[4]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

Area Under the Plasma Concentration-Time Curve (AUC) is a measure of the plasma concentration of the drug over time. The AUC 0-24hours is area under the plasma concentration-time curve from time zero through 24 hours after dosing. A compartmental model was used to measure the plasma concentrations of valganciclovir. The PK analysis population was used for the analysis. One participant was not analyzed for this outcome measure as the participant underwent both a kidney and liver transplant. Here n represents number of participant with specific transplant i.e., kidney, liver, and heart.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose; 1-3, 3-7, 7-12 hours post dose on any day between Day 7 to Day 14; and at Week 6, Week 10 and, Week 14

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this outcome measure

| End point values                     | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |  |
|--------------------------------------|------------------------------------|-------------------------------------------|-------------------------------------|--|
| Subject group type                   | Reporting group                    | Reporting group                           | Reporting group                     |  |
| Number of subjects analysed          | 17                                 | 20                                        | 25                                  |  |
| Units: mcg*hr/mL                     |                                    |                                           |                                     |  |
| arithmetic mean (standard deviation) |                                    |                                           |                                     |  |
| In kidney recipients, n=2, 12, 19    | 65.2 (± 16.6)                      | 55 (± 11.9)                               | 50 (± 11.6)                         |  |
| In liver recipients, n=9, 6, 2       | 69.4 (± 35.4)                      | 58.4 (± 6.18)                             | 35.6 (± 2.76)                       |  |
| In heart recipients, n=6, 2, 4       | 56.3 (± 23.2)                      | 60 (± 19.3)                               | 61.2 (± 26)                         |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Adverse Events Leading to Discontinuation of the Study Drug

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Adverse Events Leading to Discontinuation of the Study Drug <sup>[5]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation in participant administered a pharmaceutical product, which did not necessarily have to have a causal relationship with this treatment. The number of participants with AEs leading to dose interruptions or modifications are reported. Safety population was used for the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to Week 26

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this outcome measure.

| End point values            | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |  |
|-----------------------------|------------------------------------|-------------------------------------------|-------------------------------------|--|
| Subject group type          | Reporting group                    | Reporting group                           | Reporting group                     |  |
| Number of subjects analysed | 17                                 | 21                                        | 25                                  |  |
| Units: Participants         | 1                                  | 2                                         | 0                                   |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with 3 Grade Shift from Baseline of Adverse Events in Haematology and Serum Chemistry

|                 |                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with 3 Grade Shift from Baseline of Adverse Events in Haematology and Serum Chemistry <sup>[6]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|

End point description:

The number of participants experiencing a 3 grade shift (example from Grade 0 to Grade 3) from baseline (BL) in hematology and serum chemistry laboratory parameters are reported. Safety population included all participants who received at least one dose of valganciclovir. The data was analyzed for overall study only. Safety population was used for the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to Week 26

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this outcome measure

| End point values                | Safety population    |  |  |  |
|---------------------------------|----------------------|--|--|--|
| Subject group type              | Subject analysis set |  |  |  |
| Number of subjects analysed     | 63                   |  |  |  |
| Units: Participants             |                      |  |  |  |
| Hemoglobin low, n= 63           | 6                    |  |  |  |
| White Blood Cell low, n=59      | 3                    |  |  |  |
| Lymphocytes low, n= 54          | 3                    |  |  |  |
| Neutrophils low, n= 54          | 7                    |  |  |  |
| Potassium low, n=56             | 4                    |  |  |  |
| Potassium high, n=57            | 4                    |  |  |  |
| Alkaline Phosphatase high, n=40 | 1                    |  |  |  |
| Alanine transaminase high, n=48 | 1                    |  |  |  |
| Total Bilirubin high, n=38      | 1                    |  |  |  |
| Sodium low, n=58                | 2                    |  |  |  |
| Sodium high, n=57               | 0                    |  |  |  |
| Calcium low, n=46               | 1                    |  |  |  |
| Phosphate low, n=43             | 2                    |  |  |  |
| Fasting Glucose low, n=39       | 1                    |  |  |  |
| Uric Acid high, n=21            | 2                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with 4 Grade Shift from Baseline of Adverse Events in Haematology and Serum Chemistry

|                 |                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with 4 Grade Shift from Baseline of Adverse Events in Haematology and Serum Chemistry <sup>[7]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|

End point description:

The number of participants experiencing a 4 grade shift (example from Grade 0 to Grade 4) from BL in hematology and serum chemistry laboratory parameters are reported. The data was analyzed for overall study only. Safety population was used for the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to Week 26

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this outcome measure

| End point values                | Safety population    |  |  |  |
|---------------------------------|----------------------|--|--|--|
| Subject group type              | Subject analysis set |  |  |  |
| Number of subjects analysed     | 63                   |  |  |  |
| Units: Participants             |                      |  |  |  |
| Hemoglobin low, n= 63           | 0                    |  |  |  |
| White Blood Cell low, n=59      | 1                    |  |  |  |
| Lymphocytes low, n= 54          | 3                    |  |  |  |
| Neutrophils low, n= 54          | 4                    |  |  |  |
| Potassium low, n=56             | 0                    |  |  |  |
| Potassium high, n=57            | 2                    |  |  |  |
| Alkaline Phosphatase high, n=40 | 0                    |  |  |  |
| Alanine transaminase high, n=48 | 0                    |  |  |  |
| Total Bilirubin high, n=38      | 0                    |  |  |  |
| Sodium low, n=58                | 0                    |  |  |  |
| Sodium high, n=57               | 1                    |  |  |  |
| Calcium low, n=46               | 3                    |  |  |  |
| Phosphate low, n=43             | 0                    |  |  |  |
| Fasting Glucose low, n=39       | 0                    |  |  |  |
| Uric Acid high, n=21            | 2                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Cytomegalovirus Disease Over Time

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Number of Participants with Cytomegalovirus Disease Over Time |
|-----------------|---------------------------------------------------------------|

End point description:

Cytomegalovirus (CMV) disease is defined as syndrome or tissue invasive disease in which CMV virus was identified in blood, urine, biopsy or other suitable specimen, which could be in conjunction with one or more of the following events: a) CMV syndrome was defined as virus present in blood or other suitable specimen, plus fever, and any of the following: leukopenia, atypical lymphocytosis, thrombopenia or elevated hepatic transaminases (for non-liver recipients). b) The diagnosis of organ specific tissue invasive CMV disease was evidence of CMV in the tissue (CMV inclusion bodies or in situ detection of CMV antigen or DNA), plus signs/symptoms of organ dysfunction. Safety population was used for the analysis.

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

End point timeframe:

Up to Week 26

| End point values            | Valganciclovir age group <= 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group >= 12 years |  |
|-----------------------------|-------------------------------------|-------------------------------------------|--------------------------------------|--|
| Subject group type          | Reporting group                     | Reporting group                           | Reporting group                      |  |
| Number of subjects analysed | 17                                  | 21                                        | 25                                   |  |
| Units: Participants         | 0                                   | 2                                         | 2                                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Treatment Failures

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Number of Participants with Treatment Failures |
|-----------------|------------------------------------------------|

End point description:

Treatment failure was defined as either the development of CMV (viremia, antigenemia or test positive) requiring treatment up to day 100 post-transplant (ie, while undergoing prophylaxis with valganciclovir up to day 100) or discontinuation of study medication due to lack of efficacy or to toxicity. ITT population was used for the analysis.

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

End point timeframe:

Up to Week 26

| End point values              | Valganciclovir<br>age group <= 2 years | Valganciclovir<br>age group >2 to < 12 years | Valganciclovir<br>age group >= 12 years |  |
|-------------------------------|----------------------------------------|----------------------------------------------|-----------------------------------------|--|
| Subject group type            | Reporting group                        | Reporting group                              | Reporting group                         |  |
| Number of subjects analysed   | 17                                     | 21                                           | 25                                      |  |
| Units: Number of participants | 2                                      | 2                                            | 0                                       |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants who Experienced Graft Loss

|                 |                                                   |
|-----------------|---------------------------------------------------|
| End point title | Number of Participants who Experienced Graft Loss |
|-----------------|---------------------------------------------------|

End point description:

Graft loss was defined as impairment of organ function to such a degree that the participant died or underwent re-transplantation. The Intent to treat (ITT) population was used for analysis.

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

End point timeframe:

Up to Week 26

| End point values                 | Valganciclovir<br>age group ≤<br>2 years | Valganciclovir<br>age group >2<br>to < 12 years | Valganciclovir<br>age group ≥<br>12 years |  |
|----------------------------------|------------------------------------------|-------------------------------------------------|-------------------------------------------|--|
| Subject group type               | Reporting group                          | Reporting group                                 | Reporting group                           |  |
| Number of subjects analysed      | 17                                       | 21                                              | 25                                        |  |
| Units: Participants              |                                          |                                                 |                                           |  |
| Acute Graft Rejection            | 1                                        | 0                                               | 0                                         |  |
| Chronic Graft Rejection          | 0                                        | 0                                               | 0                                         |  |
| Recurrence of Underlying Disease | 0                                        | 0                                               | 0                                         |  |
| Technical Complications          | 0                                        | 0                                               | 1                                         |  |
| Primary Graft Non-Function       | 0                                        | 0                                               | 0                                         |  |
| Other                            | 0                                        | 1                                               | 0                                         |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Maximum Plasma Concentration of Valganciclovir Over Time

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Mean Maximum Plasma Concentration of Valganciclovir Over Time |
|-----------------|---------------------------------------------------------------|

End point description:

Maximum Plasma Concentration (C<sub>max</sub>) is defined as the maximum observed plasma concentration of Valganciclovir. Participants with kidney, liver and heart transplant were analysed. The PK analysis population was used for the analysis. One participant was not analyzed for this outcome measure as the participant underwent both a kidney and liver transplant. Here n represents number of participant with specific transplant i.e., kidney, liver, and heart.

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

End point timeframe:

Pre-dose; 1-3, 3-7, 7-12 hours post dose on any day between Day 7 to Day 14; and at Week 6, Week 10 and, Week 14

| End point values                     | Valganciclovir<br>age group ≤<br>2 years | Valganciclovir<br>age group >2<br>to < 12 years | Valganciclovir<br>age group ≥<br>12 years |  |
|--------------------------------------|------------------------------------------|-------------------------------------------------|-------------------------------------------|--|
| Subject group type                   | Reporting group                          | Reporting group                                 | Reporting group                           |  |
| Number of subjects analysed          | 17                                       | 20                                              | 25                                        |  |
| Units: mcg/mL                        |                                          |                                                 |                                           |  |
| arithmetic mean (standard deviation) |                                          |                                                 |                                           |  |
| In kidney recipients, n=2, 12, 19    | 10 (± 0.04)                              | 8.74 (± 2.49)                                   | 7.85 (± 2.1)                              |  |
| In liver recipients, n=9, 6, 2       | 11.7 (± 3.59)                            | 9.35 (± 2.33)                                   | 5.55 (± 1.34)                             |  |
| In heart recipients, n=6, 2, 4       | 8.22 (± 2.44)                            | 12.5 (± 1.02)                                   | 9.5 (± 3.34)                              |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Elimination Half-Life of Valganciclovir Over Time

|                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                              | Mean Elimination Half-Life of Valganciclovir Over Time |
| End point description:<br>The Elimination Half-Life Period is defined as the time measured for the plasma concentration to decrease by half to its original concentration. The PK analysis population was used for the analysis. One participant was not analyzed for this outcome measure as the participant underwent both a kidney and liver transplant. Here n represents number of participant with specific transplant i.e., kidney, liver, and heart. |                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary                                              |
| End point timeframe:<br>Pre-dose; 1-3, 3-7, 7-12 hours post dose on any day between Day 7 to Day 14; Week 6, and at Week 10 and, Week 14                                                                                                                                                                                                                                                                                                                     |                                                        |

| End point values                     | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |  |
|--------------------------------------|------------------------------------|-------------------------------------------|-------------------------------------|--|
| Subject group type                   | Reporting group                    | Reporting group                           | Reporting group                     |  |
| Number of subjects analysed          | 17                                 | 20                                        | 25                                  |  |
| Units: hour                          |                                    |                                           |                                     |  |
| arithmetic mean (standard deviation) |                                    |                                           |                                     |  |
| In kidney recipients, n=2, 12, 19    | 3.1 (± 0.59)                       | 4.47 (± 1.37)                             | 5.69 (± 1.06)                       |  |
| In liver recipients, n=9, 6, 2       | 2.72 (± 1.32)                      | 3.61 (± 0.8)                              | 4.5 (± 0.25)                        |  |
| In heart recipients, n=6, 2, 4       | 3.6 (± 1.73)                       | 2.62 (± 0.65)                             | 5.05 (± 0.7)                        |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Who Experienced Episodes of Rejection Over Time

|                                                                                                                                     |                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title                                                                                                                     | Number of Participants Who Experienced Episodes of Rejection Over Time |
| End point description:<br>Participants with biopsy proven active rejection were reported. ITT population was used for the analysis. |                                                                        |
| End point type                                                                                                                      | Secondary                                                              |
| End point timeframe:<br>Up to Week 26                                                                                               |                                                                        |

| End point values            | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |  |
|-----------------------------|------------------------------------|-------------------------------------------|-------------------------------------|--|
| Subject group type          | Reporting group                    | Reporting group                           | Reporting group                     |  |
| Number of subjects analysed | 17                                 | 21                                        | 25                                  |  |
| Units: Participants         | 5                                  | 2                                         | 2                                   |  |



## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 26

Adverse event reporting additional description:

Serious adverse events and non-serious adverse events are reported in safety analysis set, which consists of all participants who received at least one dose of study drug and had a safety assessment performed post baseline.

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 8.0 |
|--------------------|-----|

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Valganciclovir age group <= 2 years |
|-----------------------|-------------------------------------|

Reporting group description:

Participants aged <= 2 years received a once daily oral dose (solution or tablets) of valganciclovir from the time of kidney transplant for up to 100 days post-transplant. Dose [in milligrams (mg)] was calculated using the algorithm  $[7 * \text{Body Surface Area} * \text{Creatinine Clearance}]$ .

|                       |                                           |
|-----------------------|-------------------------------------------|
| Reporting group title | Valganciclovir age group >2 to < 12 years |
|-----------------------|-------------------------------------------|

Reporting group description:

Participants aged >2 to < 12 years received a once daily oral dose (solution or tablets) of valganciclovir from the time of kidney transplant for up to 100 days post-transplant. Dose [in milligrams (mg)] was calculated using the algorithm  $[7 * \text{Body Surface Area} * \text{Creatinine Clearance}]$ .

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Valganciclovir age group >= 12 years |
|-----------------------|--------------------------------------|

Reporting group description:

Participants aged >= 12 years received a once daily oral dose (solution or tablets) of valganciclovir from the time of kidney transplant for up to 100 days post-transplant. Dose [in milligrams (mg)] was calculated using the algorithm  $[7 * \text{Body Surface Area} * \text{Creatinine Clearance}]$ .

| Serious adverse events                                              | Valganciclovir age group <= 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group >= 12 years |
|---------------------------------------------------------------------|-------------------------------------|-------------------------------------------|--------------------------------------|
| Total subjects affected by serious adverse events                   |                                     |                                           |                                      |
| subjects affected / exposed                                         | 13 / 17 (76.47%)                    | 11 / 21 (52.38%)                          | 11 / 25 (44.00%)                     |
| number of deaths (all causes)                                       | 1                                   | 0                                         | 0                                    |
| number of deaths resulting from adverse events                      | 0                                   | 0                                         | 0                                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                     |                                           |                                      |
| Plasmablastic lymphoma                                              |                                     |                                           |                                      |
| subjects affected / exposed                                         | 0 / 17 (0.00%)                      | 1 / 21 (4.76%)                            | 0 / 25 (0.00%)                       |
| occurrences causally related to treatment / all                     | 0 / 0                               | 0 / 1                                     | 0 / 0                                |
| deaths causally related to treatment / all                          | 0 / 0                               | 0 / 0                                     | 0 / 0                                |
| Vascular disorders                                                  |                                     |                                           |                                      |
| Haematoma                                                           |                                     |                                           |                                      |

|                                                      |                |                |                 |
|------------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                          | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Lymphocele                                           |                |                |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 21 (0.00%) | 1 / 25 (4.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Surgical and medical procedures                      |                |                |                 |
| Gastrostomy tube insertion                           |                |                |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| General disorders and administration site conditions |                |                |                 |
| Pyrexia                                              |                |                |                 |
| subjects affected / exposed                          | 1 / 17 (5.88%) | 2 / 21 (9.52%) | 1 / 25 (4.00%)  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 2          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Chest pain                                           |                |                |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 21 (0.00%) | 1 / 25 (4.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Influenza like illness                               |                |                |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 21 (0.00%) | 1 / 25 (4.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Immune system disorders                              |                |                |                 |
| Transplant rejection                                 |                |                |                 |
| subjects affected / exposed                          | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 3 / 25 (12.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 4           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders      |                |                |                 |
| Asthma                                               |                |                |                 |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoxia                                         |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Stridor                                         |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Cytomegalovirus test positive                   |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Transaminases increased                         |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood creatinine increased                      |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cytomegalovirus antigen positive                |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatic enzyme increased                        |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |

|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| Subdural haematoma                              |                 |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                 |                |                |
| Cardiac failure                                 |                 |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |
| Cardiac tamponade                               |                 |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                 |                |                |
| Cerebral infarction                             |                 |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Leukoencephalopathy                             |                 |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                 |                |                |
| Anaemia                                         |                 |                |                |
| subjects affected / exposed                     | 2 / 17 (11.76%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Neutropenia                                     |                 |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 1 / 21 (4.76%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Febrile neutropenia                             |                 |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Intra–abdominal haemorrhage                     |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 2 / 21 (9.52%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal haemorrhage                    |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal hypomotility                   |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrooesophageal reflux disease                |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal perforation                          |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting                                        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Hepatic artery thrombosis                       |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bile duct stenosis                              |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholangitis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatic artery stenosis                         |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 21 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatic function abnormal                       |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Portal vein thrombosis                          |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Renal failure acute                             |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ureteric obstruction                            |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 21 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Cytomegalovirus Viraemia                        |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 2 / 21 (9.52%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Epstein–barr virus infection                    |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bacterial sepsis                                |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Biliary tract infection                         |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ear infection                                   |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal infection                      |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Liver abscess                                   |                |                |                |



|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 21 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nasopharyngitis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pharyngitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 21 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyelonephritis                                  |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis                                          |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Viral infection                                 |                |                |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Metabolic disorder                              |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Valganciclovir age group ≤ 2 years | Valganciclovir age group >2 to < 12 years | Valganciclovir age group ≥ 12 years |
|-------------------------------------------------------|------------------------------------|-------------------------------------------|-------------------------------------|
| Total subjects affected by non-serious adverse events |                                    |                                           |                                     |
| subjects affected / exposed                           | 17 / 17 (100.00%)                  | 17 / 21 (80.95%)                          | 21 / 25 (84.00%)                    |
| Vascular disorders                                    |                                    |                                           |                                     |
| Hypertension                                          |                                    |                                           |                                     |
| subjects affected / exposed                           | 4 / 17 (23.53%)                    | 6 / 21 (28.57%)                           | 8 / 25 (32.00%)                     |
| occurrences (all)                                     | 4                                  | 6                                         | 8                                   |
| Haematoma                                             |                                    |                                           |                                     |
| subjects affected / exposed                           | 1 / 17 (5.88%)                     | 0 / 21 (0.00%)                            | 0 / 25 (0.00%)                      |
| occurrences (all)                                     | 1                                  | 0                                         | 0                                   |
| General disorders and administration site conditions  |                                    |                                           |                                     |
| Pyrexia                                               |                                    |                                           |                                     |
| subjects affected / exposed                           | 5 / 17 (29.41%)                    | 8 / 21 (38.10%)                           | 4 / 25 (16.00%)                     |
| occurrences (all)                                     | 5                                  | 9                                         | 5                                   |
| Oedema Peripheral                                     |                                    |                                           |                                     |
| subjects affected / exposed                           | 0 / 17 (0.00%)                     | 0 / 21 (0.00%)                            | 5 / 25 (20.00%)                     |
| occurrences (all)                                     | 0                                  | 0                                         | 5                                   |
| Irritability                                          |                                    |                                           |                                     |
| subjects affected / exposed                           | 2 / 17 (11.76%)                    | 0 / 21 (0.00%)                            | 0 / 25 (0.00%)                      |
| occurrences (all)                                     | 2                                  | 0                                         | 0                                   |
| Catheter Site Discharge                               |                                    |                                           |                                     |
| subjects affected / exposed                           | 1 / 17 (5.88%)                     | 0 / 21 (0.00%)                            | 0 / 25 (0.00%)                      |
| occurrences (all)                                     | 1                                  | 0                                         | 0                                   |
| Catheter Site Inflammation                            |                                    |                                           |                                     |
| subjects affected / exposed                           | 1 / 17 (5.88%)                     | 0 / 21 (0.00%)                            | 0 / 25 (0.00%)                      |
| occurrences (all)                                     | 1                                  | 0                                         | 0                                   |
| Immune system disorders                               |                                    |                                           |                                     |
| Liver Transplant Rejection                            |                                    |                                           |                                     |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 17 (11.76%) | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)                               | 3               | 0               | 0               |
| Transplant Rejection                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 17 (11.76%) | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)                               | 3               | 0               | 0               |
| Milk Allergy                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)                               | 2               | 0               | 0               |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Cough                                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 5 / 21 (23.81%) | 1 / 25 (4.00%)  |
| occurrences (all)                               | 1               | 7               | 1               |
| Pharyngolaryngeal pain                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 1 / 21 (4.76%)  | 3 / 25 (12.00%) |
| occurrences (all)                               | 0               | 1               | 3               |
| Pleural Effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 2 / 21 (9.52%)  | 1 / 25 (4.00%)  |
| occurrences (all)                               | 1               | 2               | 1               |
| Rhinorrhoea                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 21 (0.00%)  | 4 / 25 (16.00%) |
| occurrences (all)                               | 0               | 0               | 5               |
| Bronchospasm                                    |                 |                 |                 |
| subjects affected / exposed                     | 3 / 17 (17.65%) | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)                               | 3               | 0               | 0               |
| Atelectasis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 1 / 25 (4.00%)  |
| occurrences (all)                               | 1               | 0               | 1               |
| Nasal Congestion                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 21 (0.00%)  | 2 / 25 (8.00%)  |
| occurrences (all)                               | 0               | 0               | 2               |
| Wheezing                                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 1 / 25 (4.00%)  |
| occurrences (all)                               | 1               | 0               | 1               |
| Pneumothorax                                    |                 |                 |                 |

|                                                                                                                               |                     |                     |                      |
|-------------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                              | 1 / 17 (5.88%)<br>2 | 0 / 21 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  |
| Stridor<br>subjects affected / exposed<br>occurrences (all)                                                                   | 1 / 17 (5.88%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  |
| Psychiatric disorders<br>Agitation<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 17 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                                                   | 0 / 17 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                                                  | 1 / 17 (5.88%)<br>1 | 1 / 21 (4.76%)<br>1 | 0 / 25 (0.00%)<br>0  |
| Investigations<br>Epstein-Barr Virus Test positive<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 17 (0.00%)<br>0 | 2 / 21 (9.52%)<br>2 | 0 / 25 (0.00%)<br>0  |
| Blood Albumin Decreased<br>subjects affected / exposed<br>occurrences (all)                                                   | 1 / 17 (5.88%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  |
| White Blood Cell Count Increased<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 17 (5.88%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  |
| Injury, poisoning and procedural complications<br>Incision site infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0 | 2 / 21 (9.52%)<br>2 | 4 / 25 (16.00%)<br>4 |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                                                           | 0 / 17 (0.00%)<br>0 | 2 / 21 (9.52%)<br>2 | 1 / 25 (4.00%)<br>1  |
| Device Failure<br>subjects affected / exposed<br>occurrences (all)                                                            | 1 / 17 (5.88%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  |
| Graft Ischaemia                                                                                                               |                     |                     |                      |

|                                                |                 |                |                 |
|------------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 1               | 0              | 0               |
| Postoperative Thoracic procedure complications |                 |                |                 |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 1               | 0              | 0               |
| Cardiac disorders                              |                 |                |                 |
| Pericardial Effusion                           |                 |                |                 |
| subjects affected / exposed                    | 0 / 17 (0.00%)  | 1 / 21 (4.76%) | 2 / 25 (8.00%)  |
| occurrences (all)                              | 0               | 1              | 2               |
| Bradycardia                                    |                 |                |                 |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 1               | 0              | 0               |
| Cardiac Disorder                               |                 |                |                 |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 1               | 0              | 0               |
| Left Ventricular Failure                       |                 |                |                 |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 1               | 0              | 0               |
| Sinus Bradycardia                              |                 |                |                 |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 1               | 0              | 0               |
| Nervous system disorders                       |                 |                |                 |
| Headache                                       |                 |                |                 |
| subjects affected / exposed                    | 0 / 17 (0.00%)  | 0 / 21 (0.00%) | 4 / 25 (16.00%) |
| occurrences (all)                              | 0               | 0              | 7               |
| Convulsion                                     |                 |                |                 |
| subjects affected / exposed                    | 2 / 17 (11.76%) | 1 / 21 (4.76%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 2               | 3              | 0               |
| Dystonia                                       |                 |                |                 |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 1               | 0              | 0               |
| Encephalomalacia                               |                 |                |                 |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%)  |
| occurrences (all)                              | 1               | 0              | 0               |
| Blood and lymphatic system disorders           |                 |                |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Anaemia                     |                 |                 |                 |
| subjects affected / exposed | 9 / 17 (52.94%) | 4 / 21 (19.05%) | 0 / 25 (0.00%)  |
| occurrences (all)           | 11              | 4               | 0               |
| Neutropenia                 |                 |                 |                 |
| subjects affected / exposed | 4 / 17 (23.53%) | 1 / 21 (4.76%)  | 1 / 25 (4.00%)  |
| occurrences (all)           | 5               | 1               | 1               |
| Leukocytosis                |                 |                 |                 |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 21 (4.76%)  | 0 / 25 (0.00%)  |
| occurrences (all)           | 3               | 1               | 0               |
| Leukopenia                  |                 |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 21 (0.00%)  | 2 / 25 (8.00%)  |
| occurrences (all)           | 0               | 0               | 2               |
| Thrombocythaemia            |                 |                 |                 |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Thrombocytopenia            |                 |                 |                 |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 1 / 25 (4.00%)  |
| occurrences (all)           | 1               | 0               | 1               |
| Lymphopenia                 |                 |                 |                 |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Gastrointestinal disorders  |                 |                 |                 |
| Diarrhoea                   |                 |                 |                 |
| subjects affected / exposed | 7 / 17 (41.18%) | 8 / 21 (38.10%) | 6 / 25 (24.00%) |
| occurrences (all)           | 7               | 15              | 7               |
| Vomiting                    |                 |                 |                 |
| subjects affected / exposed | 2 / 17 (11.76%) | 7 / 21 (33.33%) | 7 / 25 (28.00%) |
| occurrences (all)           | 2               | 8               | 7               |
| Nausea                      |                 |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%)  | 2 / 21 (9.52%)  | 6 / 25 (24.00%) |
| occurrences (all)           | 0               | 2               | 6               |
| Constipation                |                 |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%)  | 5 / 21 (23.81%) | 2 / 25 (8.00%)  |
| occurrences (all)           | 0               | 5               | 2               |
| Abdominal pain              |                 |                 |                 |

|                                        |                 |                 |                 |
|----------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed            | 1 / 17 (5.88%)  | 3 / 21 (14.29%) | 1 / 25 (4.00%)  |
| occurrences (all)                      | 1               | 3               | 2               |
| Abdominal Distention                   |                 |                 |                 |
| subjects affected / exposed            | 0 / 17 (0.00%)  | 2 / 21 (9.52%)  | 1 / 25 (4.00%)  |
| occurrences (all)                      | 0               | 2               | 1               |
| Ascites                                |                 |                 |                 |
| subjects affected / exposed            | 3 / 17 (17.65%) | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)                      | 3               | 0               | 0               |
| Gastrointestinal Haemorrhage           |                 |                 |                 |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 2 / 21 (9.52%)  | 0 / 25 (0.00%)  |
| occurrences (all)                      | 1               | 2               | 0               |
| Teething                               |                 |                 |                 |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0               |
| Hepatobiliary disorders                |                 |                 |                 |
| Biliary Tract Disorder                 |                 |                 |                 |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0               |
| Hepatic Function Abnormal              |                 |                 |                 |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%)  |
| occurrences (all)                      | 2               | 0               | 0               |
| Skin and subcutaneous tissue disorders |                 |                 |                 |
| Pruritus                               |                 |                 |                 |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 4 / 21 (19.05%) | 1 / 25 (4.00%)  |
| occurrences (all)                      | 1               | 4               | 1               |
| Rash                                   |                 |                 |                 |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 2 / 21 (9.52%)  | 2 / 25 (8.00%)  |
| occurrences (all)                      | 1               | 2               | 2               |
| Acne                                   |                 |                 |                 |
| subjects affected / exposed            | 0 / 17 (0.00%)  | 1 / 21 (4.76%)  | 3 / 25 (12.00%) |
| occurrences (all)                      | 0               | 1               | 3               |
| Dermatitis                             |                 |                 |                 |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 1 / 25 (4.00%)  |
| occurrences (all)                      | 1               | 0               | 1               |
| Dermatitis Diaper                      |                 |                 |                 |

|                                                                                                                          |                      |                      |                      |
|--------------------------------------------------------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                         | 2 / 17 (11.76%)<br>2 | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  |
| Hirsutism<br>subjects affected / exposed<br>occurrences (all)                                                            | 0 / 17 (0.00%)<br>0  | 2 / 21 (9.52%)<br>2  | 0 / 25 (0.00%)<br>0  |
| Pruritus Generalised<br>subjects affected / exposed<br>occurrences (all)                                                 | 1 / 17 (5.88%)<br>1  | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)                                                            | 1 / 17 (5.88%)<br>1  | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 17 (0.00%)<br>0  | 4 / 21 (19.05%)<br>5 | 0 / 25 (0.00%)<br>0  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                                                              | 0 / 17 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2  |
| Acute Prerenal failure<br>subjects affected / exposed<br>occurrences (all)                                               | 1 / 17 (5.88%)<br>1  | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  |
| Renal Failure<br>subjects affected / exposed<br>occurrences (all)                                                        | 1 / 17 (5.88%)<br>1  | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 17 (5.88%)<br>1  | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Pain in Extremity<br>subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1  | 3 / 25 (12.00%)<br>3 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                            | 0 / 17 (0.00%)<br>0  | 2 / 21 (9.52%)<br>2  | 0 / 25 (0.00%)<br>0  |
| Infections and infestations                                                                                              |                      |                      |                      |



|                                                                                           |                      |                      |                       |
|-------------------------------------------------------------------------------------------|----------------------|----------------------|-----------------------|
| Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all)     | 4 / 17 (23.53%)<br>5 | 5 / 21 (23.81%)<br>8 | 7 / 25 (28.00%)<br>12 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 17 (5.88%)<br>1  | 1 / 21 (4.76%)<br>1  | 3 / 25 (12.00%)<br>3  |
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all)               | 0 / 17 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1  | 4 / 25 (16.00%)<br>4  |
| Otitis Media<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 17 (5.88%)<br>1  | 0 / 21 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2   |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 17 (5.88%)<br>1  | 0 / 21 (0.00%)<br>0  | 1 / 25 (4.00%)<br>1   |
| Clostridium Colitis<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 17 (5.88%)<br>1  | 0 / 21 (0.00%)<br>0  | 1 / 25 (4.00%)<br>1   |
| Epstein-Barr Virus Infection<br>subjects affected / exposed<br>occurrences (all)          | 2 / 17 (11.76%)<br>2 | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0   |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 17 (0.00%)<br>0  | 2 / 21 (9.52%)<br>2  | 0 / 25 (0.00%)<br>0   |
| Oral Candidiasis<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 17 (11.76%)<br>2 | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0   |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 17 (0.00%)<br>0  | 2 / 21 (9.52%)<br>2  | 0 / 25 (0.00%)<br>0   |
| Respiratory Syncytial Virus Infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 17 (11.76%)<br>2 | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0   |
| Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all)           | 2 / 17 (11.76%)<br>3 | 0 / 21 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0   |

|                                    |                 |                 |                |
|------------------------------------|-----------------|-----------------|----------------|
| Sepsis                             |                 |                 |                |
| subjects affected / exposed        | 2 / 17 (11.76%) | 0 / 21 (0.00%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 4               | 0               | 0              |
| Abdominal Infection                |                 |                 |                |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0              |
| Candidiasis                        |                 |                 |                |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0              |
| Central Line Infection             |                 |                 |                |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0              |
| Para Influenzae Virus Infection    |                 |                 |                |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0              |
| Pneumonia Bacterial                |                 |                 |                |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0              |
| Staphylococcal infection           |                 |                 |                |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0              |
| Stenotrophomonas infection         |                 |                 |                |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 21 (0.00%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0              |
| Metabolism and nutrition disorders |                 |                 |                |
| Hypomagnesaemia                    |                 |                 |                |
| subjects affected / exposed        | 2 / 17 (11.76%) | 4 / 21 (19.05%) | 0 / 25 (0.00%) |
| occurrences (all)                  | 2               | 4               | 0              |
| Hyperkalaemia                      |                 |                 |                |
| subjects affected / exposed        | 3 / 17 (17.65%) | 2 / 21 (9.52%)  | 0 / 25 (0.00%) |
| occurrences (all)                  | 3               | 2               | 0              |
| Hyperglycaemia                     |                 |                 |                |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 2 / 21 (9.52%)  | 1 / 25 (4.00%) |
| occurrences (all)                  | 1               | 2               | 1              |
| Metabolic Acidosis                 |                 |                 |                |

|                             |                 |                |                |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 4 / 17 (23.53%) | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all)           | 5               | 0              | 0              |
| Hypokalaemia                |                 |                |                |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences (all)           | 3               | 1              | 0              |
| Feeding disorder            |                 |                |                |
| subjects affected / exposed | 1 / 17 (5.88%)  | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences (all)           | 1               | 1              | 0              |
| Hyperphosphataemia          |                 |                |                |
| subjects affected / exposed | 1 / 17 (5.88%)  | 1 / 21 (4.76%) | 0 / 25 (0.00%) |
| occurrences (all)           | 1               | 1              | 0              |
| Hypophosphataemia           |                 |                |                |
| subjects affected / exposed | 0 / 17 (0.00%)  | 2 / 21 (9.52%) | 0 / 25 (0.00%) |
| occurrences (all)           | 0               | 2              | 0              |
| Hyperuricaemia              |                 |                |                |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |
| Hypoalbuminaemia            |                 |                |                |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |
| Hypoglycaemia               |                 |                |                |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 21 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported