



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	v1
This version publication date	30 June 2016
First version publication date	30 June 2016

Trial information

Trial identification

Sponsor protocol code	WV16726
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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, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +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	Spain: 12
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	France: 6
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Mexico: 9
Worldwide total number of subjects	63
EEA total number of subjects	21

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	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
Arm title	Valganciclovir age group ≤ 2 years

Arm description:

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 ($7 \times$ 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.

Arm title	Valganciclovir age group >2 to < 12 years
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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.

Arm title	Valganciclovir age group ≥ 12 years
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Arm description:

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

Reporting group values	Total		
Number of subjects	63		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks)	0 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: 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: 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: 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: 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: 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: 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 ^[1]
End point description: The number of participants with adverse events 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:

[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 ^[2]
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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
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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 ^[3]
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End point description:

An adverse event (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	12	9	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 ^[4]
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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
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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.h/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 ^[5]
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End point description:

The number of participants with adverse events leading to discontinuation of the study drug is reported. Safety population was used for the analysis.

End point type	Primary
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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 ^[6]
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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. Safety population was used for the analysis.

End point type	Primary
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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 ^[7]
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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. Safety population was used for the analysis.

End point type	Primary
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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
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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
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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
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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 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: 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 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				
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
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End point description:

Maximum Plasma Concentration (C_{max}) 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
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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 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/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
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End point description:

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
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End point timeframe:

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: Participants with biopsy proven active rejection were reported. ITT 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	5	2	2	

Statistical analyses

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	8.0
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Reporting groups

Reporting group title	Valganciclovir age group <= 2 years
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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
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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
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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 %

Non-serious adverse events	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 occurrences (all)	1 / 17 (5.88%) 2	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Stridor subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 21 (0.00%) 0	2 / 25 (8.00%) 2
Anxiety subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 21 (0.00%) 0	2 / 25 (8.00%) 2
Insomnia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	1 / 21 (4.76%) 1	0 / 25 (0.00%) 0
Investigations Epstein-Barr Virus Test positive subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 21 (9.52%) 2	0 / 25 (0.00%) 0
Blood Albumin Decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
White Blood Cell Count Increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Injury, poisoning and procedural complications Incision site infection subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 21 (9.52%) 2	4 / 25 (16.00%) 4
Procedural pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 21 (9.52%) 2	1 / 25 (4.00%) 1
Device Failure subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 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 occurrences (all)	2 / 17 (11.76%) 2	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Hirsutism subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 21 (9.52%) 2	0 / 25 (0.00%) 0
Pruritus Generalised subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	4 / 21 (19.05%) 5	0 / 25 (0.00%) 0
Dysuria subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 21 (0.00%) 0	2 / 25 (8.00%) 2
Acute Prerenal failure subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Renal Failure subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Musculoskeletal and connective tissue disorders Pain in Extremity subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 21 (4.76%) 1	3 / 25 (12.00%) 3
Back pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 21 (9.52%) 2	0 / 25 (0.00%) 0
Infections and infestations			

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported