Clinical trial results:
Clinical and laboratory evaluation of acute rejection, myocyte growth, repair and oxidative stress following de novo cardiac transplant: A comparison between Tacrolimus and Cyclosporine based immunoprophylactic regimens with mycophenolic acid therapeutic drug monitoring.

Summary

EudraCT number	2015-001041-83
Trial protocol	Outside EU/EEA
Global end of trial date	18 July 2008

Results information

Result version number	v2
This version publication date	01 July 2016
First version publication date	25 July 2015
Version creation reason	• Correction of full data set Revisions to the data made and clarification of previously reported data provided.

Trial information

Trial identification

Sponsor protocol code	FKC-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00157014
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Inc
Sponsor organisation address	675 Cochrane Drive, Suite 500, Markham, Canada,
Public contact	Clinical Trial Disclosure, Astellas Pharma Canada, Inc, Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Canada, Inc, Astellas.resultsdisclosure@astellas.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?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2008
Global end of trial reached?	Yes
Global end of trial date	18 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to investigate changes in subcellular markers of growth, apoptosis, differentiation, survival, inflammation, and oxidative stress, in relationship with cellular acute rejection, in de novo cardiac transplant recipients receiving either tacrolimus or cyclosporine (CsA) as the primary immunosuppressant.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

All patients received induction therapy per institutional protocol and adjunctive immunosuppression with mycophenolate mofetil (MMF). Study treatments (tacrolimus and CsA) were administered continuously beginning no earlier than pre-transplant and no later than 10 days post-transplant. Mycophenolate mofetil (MMF) was administered peri-operatively in a pre-operative dose of 1.0 g IV/PO. The post-operative dose of MMF was given within 6 hours of transplantation at 1.0g IV/P for one week post-transplant and then 1.0g PO BID throughout the study period. Methylprednisolone was administered pre-operatively for adult patients and intra-operatively for paediatric patients. Prednisone was administered daily and was tapered slowly throughout the study. It was administered orally daily in Weeks 1 to 4: 20 mg; Week 8: 10 mg ; Week 12: 7.5 mg ; Weeks 16 to 26: 5 mg ; Weeks 27 to 52; 0-5 mg. Prednisone was discontinued after Week 26 according to the investigator’s clinical judgment. During the study, all patients were treated with statins to control lipid profiles. The drug pravastatin and simvastatin were recommended as first-line statin therapy. Patients also received antihypertensive therapy with angiotensin-converting enzyme (ACE) inhibitors as standard per protocol medical management or prophylaxis of calcineurin inhibitor-induced hypertension. Patients also received ganciclovir either orally or IV for cytomegalovirus (CMV) prophylaxis at the discretion of the investigator.

Evidence for comparator:

Tacrolimus (Tac, FK506) and cyclosporine (CsA) have played a major role in the control of acute rejection (AR) in all organ transplants. Tacrolimus-based immunoprophylaxis resulted in 50% less development of hypertension, lower cholesterol and low-density lipoprotein (LDL) - cholesterol, and better preservation of renal function in both cardiac and renal transplant recipients. The dosing of CsA, MMF, and corticosteroids was based on current standards of practice for the use of these products in immunoprophylaxis of cardiac transplant patients.

Actual start date of recruitment	10 May 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 93
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	111
EEA total number of subjects	0

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)	2
Children (2-11 years)	5
Adolescents (12-17 years)	4
Adults (18-64 years)	90
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult and pediatric (from birth) male and female de novo recipients of cadaveric heart transplants.

Pre-assignment

Screening details:

Screening (pre-transplant) period was Day -180 to -1;transplant was Day 0;Randomization conducted Days 0-10 post-transplant;133 adults were screened;100 were randomized and 17 pediatric participants were screened; 11 randomized.Patients were assigned treatment with either tacrolimus or cyclosporine in a 1:1 ratio within 10 days post-transplantatio

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Tacrolimus - Adult

Arm description:

Adult primary cadaveric heart transplant recipients randomized to immunosuppression with Tacrolimus 0.05 – 0.10 mg/ kg/ day administered orally in 2 divided doses starting within 10 days of transplant.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus-Adult Dose
Investigational medicinal product code	FK506
Other name	Prograf®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Adult Dose: Tacrolimus 0.05 to 0.10 mg/kg/day in 2 divided doses starting within 10 days of transplant supplied as 5-, 1-, or 0.5-mg capsules. Tacrolimus was administered on an empty stomach, 1 hour before or 2 hours after meals. Study treatments were administered continuously beginning no earlier than pre-transplant and no later than 10 days post-transplant.In the event that therapeutic levels could not be achieved with oral capsules in the immediate post-operative period, use of commercially–obtained tacrolimus intravenous (IV) solution (Prograf® IV 5mg/mL) was permitted.

Arm title	Cyclosporine – Adult

Arm description:

Adult primary cadaveric heart transplant recipients randomized to immunosuppression with Cyclosporine 3-5 mg/kg/day administered orally in 2 divided doses starting within 10 days of transplant.

Arm type	Experimental
Investigational medicinal product name	Cyclosporine-Adult
Investigational medicinal product code	
Other name	Neoral
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Adult Dose: Starting within 10 days of transplant supplied as 10-, 25-, 50-, or 100-mg capsules. Study treatments were administered continuously beginning no earlier than pre-transplant and no later than 10 days post-transplant. In the event that therapeutic levels could not be achieved with oral capsules in the immediate post-operative period, use of commercially–obtained CsA IV solution (Sandimmune® IV 50 mg/mL) was permitted.

Arm title	Tacrolimus – Pediatric

Arm description:

Pediatric primary cadaveric heart transplant transplant recipients randomized to immunosuppression with Tacrolimus 0.05-0.30 mg/kg/day administered orally in 2 or 3 divided doses starting within 10 days of transplant.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus-Pediatric Dose
Investigational medicinal product code	FK506
Other name	Prograf®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pediatric Dose: Oral Prograf® 0.05-0.30 mg/kg/day was given in two divided doses, beginning no earlier than pre-transplant and no later than day 10 post-transplant. Tacrolimus was administered on an empty stomach, 1 hour before or 2 hours after meals. Tacrolimus may have been administered via nasogastric tube. Intravenous administration of tacrolimus should have been undertaken only when therapeutic levels could be achieved via oral and enteric routes. Intravenous dosing of tacrolimus, if required, is by administration as a continuous 24-hour infusion. Tacrolimus IV solution should be diluted in 0.9% sodium chloride or 5% dextrose for injection and stored in a glass bottle or non-polyvinyl chloride (PVC) bag for no longer than 24 hours prior to infusion. Dose decreases for mild intolerance should be based on balancing other clinical assessments, e.g., acute rejection.

Arm title	Cyclosporine – Pediatric

Arm description:

Pediatric primary cadaveric heart transplant transplant recipients randomized to immunosuppression with Cyclosporine 6-10 mg/kg/day in 2 or 3 divided doses starting within 10 days of transplant.

Arm type	Active comparator
Investigational medicinal product name	Cyclosporine - Pediatric Dose
Investigational medicinal product code	
Other name	Neoral®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pediatric Dose: Pediatric patients: Administration of the Neoral® form of cyclosporine must start within the first 10 days post transplant. It will be given at a starting dose of 6-10 mg/kg per day orally in 2 or 3 divided doses based on actual body weight unless the patient has significant renal dysfunction. The dose will subsequently be adjusted to achieve the targeted blood levels. Intravenous dosing of cyclosporine, if required, is to be initiated as a continuous 24-hour infusion of 1-2 mg/kg over 24 hours. For IV administration 1 mg/kg of IV cyclosporine should be diluted in 0.9% sodium chloride for injection or 5% dextrose for injection and stored in a glass bottle for no greater than 24 hours prior to infusion. The cyclosporine dose should be decreased in the presence of adverse events as clinically warranted. Dose decreases for mild intolerance should be based on balancing other clinical assessments, for example, acute rejection.

Number of subjects in period 1	Tacrolimus - Adult	Cyclosporine – Adult	Tacrolimus – Pediatric
Started	52	46	5
Completed	45	41	4
Not completed	7	5	1
Patient withdrawn at investigator's discretion	1	-	-
Patient living in a nursing home unable to return	1	-	-
Death	4	2	1
Patient would not have received transplant	-	1	-

Physician Discretion	-	1	-
Medications withdrawn on request of family	-	1	-
Consent withdrawn by subject	1	-	-

Number of subjects in period 1	Cyclosporine – Pediatric
Started	6
Completed	5
Not completed	1
Patient withdrawn at investigator's discretion	-
Patient living in a nursing home unable to return	-
Death	1
Patient would not have received transplant	-
Physician Discretion	-
Medications withdrawn on request of family	-
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall Study
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two patients randomized for tacrolimus were excluded from the Treatment Exposure Population (1 never received drug; 1 received incorrect drug without a waiver).

Reporting group values	Overall Study	Total	
Number of subjects	109	109	
Age, Customized Units: Participants			
0 - 2 Years	2	2	
2 - 10 Years	3	3	
10 - 18 Years	6	6	
18 - 49 Years	32	32	
50 - 59 Years	33	33	
60 - 69 Years	30	30	
70 Years and Older	3	3	
Gender categorical Units: Subjects			
Female	27	27	
Male	82	82	
Race / Ethnicity Units: Subjects			
European descent/ White	97	97	
Black	7	7	
East Indian	3	3	
Latin American	1	1	
Aboriginal	1	1	

End points

End points reporting groups

Reporting group title	Tacrolimus - Adult
Reporting group description:	
Adult primary cadaveric heart transplant recipients randomized to immunosuppression with Tacrolimus 0.05 – 0.10 mg/ kg/ day administered orally in 2 divided doses starting within 10 days of transplant.	
Reporting group title	Cyclosporine – Adult
Reporting group description:	
Adult primary cadaveric heart transplant recipients randomized to immunosuppression with Cyclosporine 3-5 mg/kg/day administered orally in 2 divided doses starting within 10 days of transplant.	
Reporting group title	Tacrolimus – Pediatric
Reporting group description:	
Pediatric primary cadaveric heart transplant transplant recipients randomized to immunosuppression with Tacrolimus 0.05-0.30 mg/kg/day administered orally in 2 or 3 divided doses starting within 10 days of transplant.	
Reporting group title	Cyclosporine – Pediatric
Reporting group description:	
Pediatric primary cadaveric heart transplant transplant recipients randomized to immunosuppression with Cyclosporine 6-10 mg/kg/day in 2 or 3 divided doses starting within 10 days of transplant.	
Subject analysis set title	Tacrolimus - Pediatric
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Pediatrics: 0.05 - 0.30 mg/ kg/ day in 2-3 divided doses starting within 10 days of transplant	
Subject analysis set title	Cyclosporine – Pediatric
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Pediatrics: 6 - 10 mg/ kg/ day in 2-3 divided doses starting within 10 days of transplant	
Subject analysis set title	Cyclosporine - Adult
Subject analysis set type	Full analysis
Subject analysis set description:	
Adults: 3-5 mg/ kg/ day in 2 divided doses starting within 10 days of transplant	
Subject analysis set title	Tacrolimus – Adult
Subject analysis set type	Full analysis
Subject analysis set description:	
Adults: 0.05 – 0.10 mg/ kg/ day in 2 divided doses starting within 10 days of transplant	

Primary: The change in the markers of growth, apoptosis, inflammation and oxidation measured in endomyocardial biopsies (TE)

End point title	The change in the markers of growth, apoptosis, inflammation and oxidation measured in endomyocardial biopsies (TE)[1][2]
End point description:	
The markers assessed were p-ERK ½ (phosphorylated extracellular signal-regulated kinase), p-JNK (phosphorylated jun N-terminal kinase) and p-p38 MAPK (phosphorylated mitogen-activated protein kinase). The data for each biopsy marker were expressed as a ratio of its densitometry / densitometry of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Change is defined as Week 52 assessment- Week 2 assessment. The number of participants analyzed per arm represents Treatment Exposure (TE) Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each marker is noted in the category titles, as "N".	
End point type	Primary
End point timeframe:	
2 Weeks and 52 Weeks	

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: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: Densitometry / Densitometry of GAPDH				
arithmetic mean (standard deviation)				
p-ERK ½ - Week 2 (N=36; 37)	0.7 (± 0.5)	0.9 (± 0.641)		
p-ERK ½ - Week 52 (N=30; 27)	0.87 (± 0.539)	0.79 (± 0.674)		
p-ERK ½ - Change from Week 2 (N=26; 25)	0.05 (± 0.834)	-0.05 (± 0.662)		
p-JNK - Week 2 (N=36; 37)	1.1 (± 0.813)	1.23 (± 0.722)		
p-JNK - Week 52 (N=30; 27)	1.33 (± 0.89)	1.46 (± 0.792)		
p-JNK - Change from Week 2 (N=26; 25)	0.03 (± 1.188)	0.22 (± 0.957)		
p-p38 MAPK - Week 2 (N=35; 37)	0.48 (± 0.45)	0.54 (± 0.556)		
p-p38 MAPK - Week 52 (N=28; 27)	0.63 (± 0.664)	0.77 (± 0.717)		
p-p38 MAPK - Change from Week 2 (N=25; 25)	0.14 (± 0.733)	0.23 (± 0.828)		

Statistical analyses

No statistical analyses for this end point

Primary: The change in the markers of growth, apoptosis, inflammation and oxidation measured in endomyocardial biopsies (Pediatric Population)

End point title	The change in the markers of growth, apoptosis, inflammation and oxidation measured in endomyocardial biopsies (Pediatric Population)[3][4]

End point description:

The markers assessed were p-ERK ½, p-JNK and p-p38 MAPK.The data for each biopsy marker were expressed as a ratio of its densitometry / densitometry of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Change is defined as Week 52 assessment- Week 2 assessment. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each marker is noted in the category titles, as "N".

End point type	Primary

End point timeframe:

2 Weeks and 52 Weeks

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: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Densitometry / Densitometry of GAPDH				
arithmetic mean (standard deviation)				
p-ERK ½ - Week 2 (N=3; 5)	1.74 (± 0.972)	1.67 (± 0.682)		
p-ERK ½ - Week 52 (N= 2; 4)	0.93 (± 0.184)	1.22 (± 0.633)		
p-ERK ½ - Change from Week 2 (N= 1; 3)	-0.09 (± 0)	-0.27 (± 0.309)		
p-JNK - Week 2 (N=3; 5)	1.17 (± 0.42)	0.91 (± 0.43)		
p-JNK - Week 52 (N= 2; 4)	0.57 (± 0.085)	0.82 (± 0.537)		
p-JNK - Change from Week 2 (N=1; 3)	-0.21 (± 0)	0.04 (± 0.189)		
p-p38 MAPK - Week 2 (N=3; 5)	0.83 (± 0.467)	0.43 (± 0.364)		
p-p38 MAPK - Week 52 (N=2; 4)	0.24 (± 0.014)	0.58 (± 0.432)		
p-p38 MAPK - Change from Week 2 (N=1; 3)	-0.04 (± 0)	0.34 (± 0.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: MCP-1 (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: MCP-1 (TE)[5]

End point description:

Change is defined as Week 52 assessment – Pre-Transplant assessment. MCP-1= monocyte chemoattractant protein-1. The number of participants analyzed per arm represents Treatment Exposure (TE) Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: pg/mL				
arithmetic mean (standard deviation)				

Pre-Transplant (N=48; 44)	233.05 (± 292.832)	193.63 (± 144.696)		
Week 52 (N=42; 40)	229.96 (± 263.084)	180.9 (± 145.067)		
Change from Pre-Transplant at Week 52 (N=42; 40)	42.92 (± 165.517)	-16.49 (± 126.586)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: s-ICAM (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: s-ICAM (TE)[6]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. s-ICAM= soluble-intracellular adhesion molecule. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 50; 45)	766.58 (± 449.572)	674.46 (± 429.036)		
Week 52 (N= 41; 40)	590.3 (± 369.942)	503.71 (± 305.531)		
Change from Pre-Transplant at Week 52 (N= 41; 40)	-227.58 (± 366.136)	-183.96 (± 250.382)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: E-selectin (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: E-selectin (TE)[7]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 50; 43)	90.4 (± 72.801)	98.96 (± 89.153)		
Week 52 (N= 41; 40)	68.6 (± 51.911)	80.93 (± 70.383)		
Change from Pre-Transplant at Week 52 (N= 41; 40)	-18.58 (± 48.247)	-19.16 (± 52.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Homocysteine (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Homocysteine (TE)[8]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: µmol/L				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 50; 44)	14.2 (± 6.94)	15.9 (± 6.97)		
Week 52 (N= 40; 40)	13.5 (± 4.19)	15.8 (± 5.33)		
Change from Pre-Transplant at Week 52 (N= 40; 40)	0.3 (± 5.02)	0.7 (± 7.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: hsCRP (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: hsCRP (TE)[9]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. hsCRP= high-sensitivity C Reactive Protein. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: mg/L				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 49; 45)	32.85 (± 50.859)	21.83 (± 33.547)		
Week 52 (N= 42; 40)	3.01 (± 3.313)	3.95 (± 5.273)		
Change from Pre-Transplant at Week 52 (N= 42; 40)	-34.32 (± 54.257)	-18.69 (± 35.354)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth,

apoptosis, differentiation and survival: F2 isoprostanes (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: F2 isoprostanes (TE)[10]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: pg/mL				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 48; 45)	52.03 (± 76.09)	53.94 (± 78.476)		
Week 52 (N= 42; 40)	30.08 (± 25.905)	50.44 (± 68.416)		
Change from Pre-Transplant at Week 52 (N= 42; 40)	-13.29 (± 40.543)	-3.43 (± 103.457)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: T-bars (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: T-bars (TE)[11]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. T-bars = thiobarbituric acid reactive substances. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: nmol/mL				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 50; 45)	3.78 (± 1.586)	3.91 (± 2.059)		
Week 52 (N= 40; 39)	3.25 (± 1.365)	3.14 (± 1.198)		
Change from Pre-Transplant at Week 52 (N= 40; 39)	-0.64 (± 1.724)	-0.77 (± 2.182)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Nitrotyrosine (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Nitrotyrosine (TE)[12]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received (TE) regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: nM				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 50; 45)	422.63 (± 393.554)	482.43 (± 390.702)		
Week 52 (N= 41; 39)	451.88 (± 443.372)	368.95 (± 262.693)		
Change from Pre-Transplant at Week 52 (N= 41; 39)	71.44 (± 332.351)	-99.79 (± 228.268)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: GSH/GSSG (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: GSH/GSSG (TE)[13]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. GSH/GSSG= ratio of reduced to oxidised glutathione.The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: Ratio				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 49; 45)	55.07 (± 62.78)	58.83 (± 71.289)		
Week 52 (N= 39; 38)	51.69 (± 55.721)	53.72 (± 55.264)		
Change from Pre-Transplant at Week 52 (N= 39; 38)	-2.07 (± 70.036)	-5.55 (± 80.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: BNP (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: BNP (TE)[14]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. BNP= Brain Natriuretic Peptide. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: ng/L				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 49; 44)	4314.8 (± 4861.78)	4240.8 (± 4673.72)		
Week 52 (N= 42; 40)	670.1 (± 1053.21)	1856.8 (± 5077.26)		
Change from Pre-Transplant at Week 52 (N= 42; 40)	-4018.4 (± 5043.28)	-1446.7 (± 6460.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Troponin T (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Troponin T (TE)[15]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. The number of participants analyzed per arm represents Treatment Exposure (TE) Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: ug/L				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 49; 44)	0.3 (± 0.686)	0.28 (± 0.878)		
Week 52 (N= 42; 40)	0.03 (± 0.116)	0.04 (± 0.12)		
Change from Pre-Transplant at Week 52 (N= 42; 40)	-0.32 (± 0.768)	-0.27 (± 0.958)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Osteopontin (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Osteopontin (TE)[16]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 50; 44)	11.88 (± 9.528)	11.14 (± 12.278)		
Week 52 (N= 41; 38)	8.77 (± 10.462)	10.49 (± 8.987)		
Change from Pre-Transplant at Week 52 (N= 41; 38)	-2.22 (± 10.615)	0.2 (± 11.158)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Fibrinogen (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Fibrinogen (TE)[17]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment.

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: g/L				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 48; 44)	4.4 (± 1.27)	4.4 (± 1.23)		
Week 52 (N= 40; 40)	3.4 (± 0.87)	3.8 (± 0.77)		
Change from Pre-Transplant at Week 52 (N= 40; 40)	-1.1 (± 1.48)	-0.5 (± 1.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: IL-6 (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: IL-6 (TE)[18]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. IL= Interleukin
The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: pg/mL				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 48; 45)	3.36 (± 4.221)	2.54 (± 3.159)		

Week 52 (N= 42; 40)	0.98 (± 0.743)	0.9 (± 0.651)		
Change from Pre-Transplant at Week 52 (N= 42; 40)	-2.84 (± 4.635)	-1.56 (± 3.146)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: IL-18 (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: IL-18 (TE)[19]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: pg/mL				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 48; 45)	574 (± 291.89)	496.2 (± 246.9)		
Week 52 (N= 40; 40)	534.6 (± 290.38)	427.2 (± 217.07)		
Change from Pre-Transplant at Week 52 (N=40; 40)	5.2 (± 289.66)	-71 (± 243.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Cystatin-C (TE)

End point title	Changes in circulating markers of inflammation, oxidation, growth, apoptosis, differentiation and survival: Cystatin-C (TE)

	[20]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. The number of participants included in the calculation for each row is noted in the category titles, as "N".

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: mg/L				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 49; 45)	1.21 (± 0.414)	1.29 (± 0.49)		
Week 52 (N= 42; 40)	1.29 (± 0.533)	1.48 (± 0.714)		
Change from Pre-Transplant at Week 52 (N= 42; 40)	0.06 (± 0.464)	0.27 (± 0.744)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Acute Rejection Episodes by International Society of Heart and Lung Transplantation (ISHLT) Criteria (TE)

End point title	Number of Acute Rejection Episodes by International Society of Heart and Lung Transplantation (ISHLT) Criteria (TE)[21]

End point description:

Acute rejection was defined as a rejection with ISHLT Grade ≥3A or by the presence of hemodynamic compromise. ISHLT Grades ≥3A include: Multifocal Moderate Rejection; Diffuse, Borderline Severe Acute Rejection; and Severe Acute Rejection. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation.

Patients may report more than one acute rejection.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: Rejection Episodes				
number (not applicable)				
Total Acute Rejection Episodes	8	8		
Acute Rejection Episodes with ISHLT Grade ≥3A	3	7		
Acute Rejection Episodes w/ Hemodynamic Compromise	6	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first acute rejection episode following de novo cardiac transplant (TE)

End point title	Time to first acute rejection episode following de novo cardiac transplant (TE)[22]

End point description:

Acute Rejection was defined as a rejection with ISHLT Grade ≥3A or by the presence of hemodynamic compromise. ISHLT Grades ≥3A include: Multifocal Moderate Rejection; Diffuse, Borderline Severe Acute Rejection; and Severe Acute Rejection. Time to first acute rejection is defined as: date of onset - date of transplant.The population analyzed represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation. Only participants who experienced acute rejection were included in the analysis.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Cyclosporine – Adult	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: Days				
arithmetic mean (standard deviation)	166.6 (± 132.86)	55 (± 35.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients requiring antilymphocyte antibodies or steroids for treatment of severe acute rejection

End point title	Number of patients requiring antilymphocyte antibodies or steroids for treatment of severe acute rejection[23]

End point description:

Severe Acute Rejection is defined as rejection with ISHLT Grade 4.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: Patients				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of cardiac rejection episodes requiring treatment (TE)

End point title	Number of cardiac rejection episodes requiring treatment

End point description:

The number of rejection episodes requiring treatment (medications started/ stopped, non-medication treatment, or both) regardless of biopsy grade or presence of hemodynamic compromise. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: Rejection Episodes				
number (not applicable)	12	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cases of acute rejection (MCAR) per patient

End point title	Mean cases of acute rejection (MCAR) per patient[25]

End point description:

MCAR represents the average number of acute rejections among all patients in each treatment group. Results were based on rejection episodes with endomyocardial biopsies.
Acute rejection was defined as a rejection with ISHLT Grade ≥3A or by the presence of hemodynamic compromise. ISHLT Grades ≥3A include: Multifocal Moderate Rejection; Diffuse, Borderline Severe Acute Rejection; and Severe Acute Rejection. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: MCAR per patient				
arithmetic mean (standard deviation)	0.15 (± 0.46)	0.17 (± 0.38)		

Statistical analyses

Statistical analysis title	Mean Cases of Acute Rejection (MCAR)
Comparison groups	Tacrolimus - Adult v Cyclosporine – Adult
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4725 [26]
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %

Notes:

[26] - No adjustments for multiple comparisons were performed.

Secondary: Number of patients with successful steroid taper or withdrawal at weeks 26 and 52 (TE)

End point title	Number of patients with successful steroid taper or withdrawal at weeks 26 and 52 (TE)

End point description:

A successful steroid taper or withdrawal was defined as steroids (prednisone) being discontinued or tapered to the suggested dose level after week 26. The number of participants analyzed per arm represents Treatment Exposure Population- defined as all patients receiving at least 1 dose of study medication summarized according to treatment received regardless of randomization allocation.

End point type	Secondary

End point timeframe:

26 Weeks and 52 Weeks

End point values	Cyclosporine - Adult	Tacrolimus – Adult		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	52		
Units: Patients				
number (not applicable)				
Week 26	16	22		
Week 52	29	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with treatment failure and crossover for treatment failure

End point title	Number of patients with treatment failure and crossover for treatment failure[27]

End point description:

Treatment failure was defined as death, re-transplantation, withdrawal due to an Adverse Event, or a switch of main immunosuppressant medication, whichever came first.

Crossover was defined as a switch from originally administered primary immunosuppressant (tacrolimus or cyclosporine) to the alternate primary immunosuppressant.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to adult population which is why arms representing only adult population are selected for this endpoint.

End point values	Tacrolimus - Adult	Cyclosporine – Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	46		
Units: Patients				
number (not applicable)				
Treatment Failures	6	11		
Crossover for Treatment Failures	2	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation and oxidation: F2 isoprostanes (Pediatric Population)

End point title	Changes in circulating markers of inflammation and oxidation: F2 isoprostanes (Pediatric Population)[28]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: pg/mL				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 5; 5)	106.06 (± 37.974)	104.68 (± 53.812)		
Week 52 (N= 3; 4)	69.71 (± 38.62)	66.48 (± 33.298)		
Change from Pre-Transplant at Week 52 (N= 3; 4)	-38.31 (± 47.563)	-30.07 (± 80.246)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation and oxidation: nitrotyrosine (Pediatric Population)

End point title	Changes in circulating markers of inflammation and oxidation: nitrotyrosine (Pediatric Population)[29]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: nM				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 5; 5)	233.08 (± 211.491)	12701.21 (± 21666.231)		
Week 52 (N= 3; 4)	5462.99 (± 7988.134)	41147.62 (± 37565.74)		
Change from Pre-Transplant at Week 52 (N= 3; 4)	5148.42 (± 7849.554)	21514.62 (± 49626.968)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation and oxidation: hsCRP (Pediatric Population)

End point title	Changes in circulating markers of inflammation and oxidation: hsCRP (Pediatric Population)[30]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: mg/L				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 5; 4)	30.46 (± 32.274)	12.08 (± 14.771)		

Week 52 (N= 3; 4)	26.31 (± 45.109)	2.43 (± 1.348)		
Change from Pre-Transplant at Week 52 (N= 3; 4)	-7.85 (± 78.126)	-13.94 (± 16.461)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in circulating markers of inflammation and oxidation: Cystatin-C (Pediatric Population)

End point title	Changes in circulating markers of inflammation and oxidation: Cystatin-C (Pediatric Population)[31]

End point description:

Change is defined as Week 52 assessment - Pre-Transplant assessment

End point type	Secondary

End point timeframe:

Pre-Transplant and 52 Weeks

Notes:

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

Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: mg/L				
arithmetic mean (standard deviation)				
Pre-Transplant (N= 5; 4)	0.86 (± 0.248)	0.77 (± 0.194)		
Week 52 (N= 3; 4)	0.87 (± 0.133)	0.84 (± 0.111)		
Change from Pre-Transplant at Week 52 (N= 3; 4)	-0.11 (± 0.197)	-0.01 (± 0.108)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Acute Rejection Episodes by International Society of Heart and Lung Transplantation (ISHLT) Criteria (Pediatric Population)

End point title	Number of Acute Rejection Episodes by International Society of Heart and Lung Transplantation (ISHLT) Criteria (Pediatric Population)[32]

End point description:

Acute rejection was defined as a rejection with ISHLT Grade ≥3A or by the presence of hemodynamic compromise.

ISHLT Grades ≥3A include: Multifocal Moderate Rejection; Diffuse, Borderline Severe Acute Rejection; and Severe Acute Rejection.

Patients may report more than one rejection episode.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Cyclosporine – Pediatric	Tacrolimus - Pediatric		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	5		
Units: Rejection Episodes				
number (not applicable)				
Total Acute Rejection Episodes	3	3		
Acute Rejection Episodes with ISHLT Grade ≥3A	3	3		
Acute Rejection Episodes w/ Hemodynamic Compromise	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first acute rejection episode following de novo cardiac transplant (Pediatric Population)

End point title	Time to first acute rejection episode following de novo cardiac transplant (Pediatric Population)[33]

End point description:

Acute Rejection was defined as a rejection with ISHLT Grade ≥3A or by the presence of hemodynamic compromise.

ISHLT Grades ≥3A include: Multifocal Moderate Rejection; Diffuse, Borderline Severe Acute Rejection; and Severe Acute Rejection.

Time to first acute rejection is defined as: date of onset - date of transplant.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Cyclosporine – Pediatric			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Days				
arithmetic mean (standard deviation)	49 (± 15.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients requiring antilymphocyte antibodies or steroids for treatment of severe acute rejection (Pediatric Population)

End point title	Number of patients requiring antilymphocyte antibodies or steroids for treatment of severe acute rejection (Pediatric Population)[34]

End point description:

Severe Acute Rejection was defined as rejection with ISHLT Grade 4.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Patients				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of cardiac rejection episodes requiring treatment (Pediatric Population)

End point title	Number of cardiac rejection episodes requiring treatment (Pediatric Population)[35]

End point description:

A summary of rejection episodes requiring treatment regardless of biopsy grade or presence of hemodynamic compromise.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Rejection Episodes				
number (not applicable)	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cases of acute rejection (MCAR) per patient (Pediatric Population)

End point title	Mean cases of acute rejection (MCAR) per patient (Pediatric Population)[36]

End point description:

MCAR represents the average number of acute rejections among all patients in each treatment group. Results were based on rejection episodes with endomyocardial biopsies.

Acute rejection was defined as a rejection with ISHLT Grade ≥3A or by the presence of hemodynamic compromise.

ISHLT Grades ≥3A include: Multifocal Moderate Rejection; Diffuse, Borderline Severe Acute Rejection; and Severe Acute Rejection.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: MCAR per patient				
arithmetic mean (standard deviation)	0.6 (± 0.55)	0.5 (± 0.55)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Tacrolimus – Pediatric v Cyclosporine – Pediatric

Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8373 [37]
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %

Notes:

[37] - No adjustments for multiple comparisons were performed.

Secondary: Number of patients with successful steroid taper or withdrawal at weeks 26 and 52 (Pediatric Population)

End point title	Number of patients with successful steroid taper or withdrawal at weeks 26 and 52 (Pediatric Population)[38]

End point description:

A successful steroid taper or withdrawal was defined as steroids (prednisone) being discontinued or tapered to the suggested dose level after week 26.

End point type	Secondary

End point timeframe:

26 Weeks and 52 Weeks

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Tacrolimus – Pediatric	Cyclosporine – Pediatric		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Patients				
number (not applicable)				
Week 26	2	3		
Week 52	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with treatment failure and crossover for treatment failure (Pediatric Population)

End point title	Number of patients with treatment failure and crossover for treatment failure (Pediatric Population)[39]

End point description:

Treatment failure was defined as death, re-transplantation, withdrawal due to an Adverse Event, or a switch of main immunosuppressant medication, whichever came first.

Crossover was defined as a switch from originally administered primary immunosuppressant (tacrolimus or cyclosporine) to the alternate primary immunosuppressant.

End point type	Secondary

End point timeframe:

52 Weeks

Notes:

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

Justification: Summary statistical analysis is only applicable to pediatric population which is why arms representing only pediatric population are selected for this endpoint.

End point values	Cyclosporine – Pediatric	Tacrolimus - Pediatric		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	5		
Units: Patients				
number (not applicable)				
Treatment Failures	3	1		
Crossover for Treatment Failures	3	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
After the initiation of study drug up to 30 days after the last dose of study drug.	
Adverse event reporting additional description:	
Treatment Emergent Adverse Events were reported. Within a preferred term, participants were counted once.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	8.0

Reporting groups	
Reporting group title	Tacrolimus - Adult
Reporting group description:	
Adults: 0.05 – 0.10 mg/ kg/ day in 2 divided doses starting within 10 days of transplant	
Reporting group title	Cyclosporine – Pediatric
Reporting group description:	
Pediatrics: 6 – 10 mg/ kg/ day in 2-3 divided doses starting within 10 days of transplant	
Reporting group title	Cyclosporine – Adult
Reporting group description:	
Adults: 3-5 mg/ kg/ day in 2 divided doses starting within 10 days of transplant	
Reporting group title	Tacrolimus – Pediatric
Reporting group description:	
Pediatrics: 0.05 – 0.30 mg/ kg/ day in 2-3 divided doses starting within 10 days of transplant	

Serious adverse events	Tacrolimus - Adult	Cyclosporine – Pediatric	Cyclosporine – Adult
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 52 (40.38%)	5 / 6 (83.33%)	24 / 46 (52.17%)
number of deaths (all causes)	4	1	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer stage III			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung neoplasm malignant			

subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Lymphoproliferative disorder			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	0 / 46 (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
Inferior vena caval occlusion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal arteritis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter related complication			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chest pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Heart transplant rejection			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Transplant rejection			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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

Pleural effusion			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory alkalosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Respiratory failure			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Injury, poisoning and procedural			

complications			
Haemothorax			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	0 / 46 (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
Atrioventricular block complete			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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 arrest			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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

Pericardial effusion			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis constrictive			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Right ventricular failure			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Supraventricular tachycardia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cerebrovascular accident			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 52 (1.92%)	2 / 6 (33.33%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			

subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Hydrocephalus			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Encephalopathy			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Partial seizures			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Syncope vasovagal			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension headache			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Neutropenia			

subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness cortical			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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 haemorrhage			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	0 / 46 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth ulceration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic disorder			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	0 / 46 (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
Vomiting			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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			
Cholelithiasis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			

subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Infections and infestations			
American trypanosomiasis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Bronchopneumonia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Cellulitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Cytomegalovirus gastritis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Cytomegalovirus infection			

subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Diverticulitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	0 / 46 (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
Pneumonia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Sinusitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (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	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (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

Serious adverse events	Tacrolimus – Pediatric		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer stage III			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphoproliferative disorder			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inferior vena caval occlusion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Temporal arteritis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vascular pseudoaneurysm				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Catheter related complication				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Heart transplant rejection				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transplant rejection				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory alkalosis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Acute respiratory distress syndrome			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Haemothorax			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural haematoma			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericarditis constrictive				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac tamponade				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral infarction				

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope vasovagal				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tension headache				

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Pancytopenia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Deafness unilateral				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Blindness cortical				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal discomfort				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mouth ulceration				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic disorder				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholelithiasis				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Acne				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephropathy toxic				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Endocrine disorders			
Adrenal mass			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
American trypanosomiasis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus gastritis				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Klebsiella bacteraemia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mediastinitis				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia klebsiella				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				

subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tacrolimus - Adult	Cyclosporine – Pediatric	Cyclosporine – Adult
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 52 (100.00%)	6 / 6 (100.00%)	46 / 46 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 52 (40.38%)	4 / 6 (66.67%)	26 / 46 (56.52%)
occurrences (all)	25	4	29
Hypotension			
subjects affected / exposed	13 / 52 (25.00%)	0 / 6 (0.00%)	7 / 46 (15.22%)
occurrences (all)	15	0	10
Surgical and medical procedures			
Removal of foreign body			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	5	0	2
Chest pain			

subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	4	0	2
Chills			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	1	0	3
Fatigue			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	7 / 46 (15.22%)
occurrences (all)	4	0	10
Hyperthermia			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	3	0	4
Influenza like illness			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Oedema Peripheral			
subjects affected / exposed	21 / 52 (40.38%)	2 / 6 (33.33%)	21 / 46 (45.65%)
occurrences (all)	32	2	24
Pyrexia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 6 (33.33%)	4 / 46 (8.70%)
occurrences (all)	5	3	5
Oedema			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	2	0	5
Cough			
subjects affected / exposed	9 / 52 (17.31%)	0 / 6 (0.00%)	6 / 46 (13.04%)
occurrences (all)	12	0	8
Dyspnoea			

subjects affected / exposed	8 / 52 (15.38%)	0 / 6 (0.00%)	5 / 46 (10.87%)
occurrences (all)	11	0	7
Pleural effusion			
subjects affected / exposed	10 / 52 (19.23%)	0 / 6 (0.00%)	18 / 46 (39.13%)
occurrences (all)	11	0	21
Pneumothorax			
subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	5	0	4
Aspiration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Respiratory distress			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	4	0	4
Anxiety			
subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	5 / 46 (10.87%)
occurrences (all)	5	0	6
Confusional state			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences (all)	3	0	1
Insomnia			
subjects affected / exposed	8 / 52 (15.38%)	1 / 6 (16.67%)	12 / 46 (26.09%)
occurrences (all)	9	1	12
Depression			
subjects affected / exposed	6 / 52 (11.54%)	1 / 6 (16.67%)	5 / 46 (10.87%)
occurrences (all)	6	1	5
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	5 / 46 (10.87%)
occurrences (all)	2	0	9
Cardiac murmur			

subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	3	0	5
Hepatic enzyme increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
Weight decreased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Weight increased			
subjects affected / exposed	10 / 52 (19.23%)	0 / 6 (0.00%)	9 / 46 (19.57%)
occurrences (all)	10	0	9
Cytomegalovirus antigen positive			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Epstein-Barr virus antibody positive			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
White blood cell count increased			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	1 / 46 (2.17%)
occurrences (all)	1	1	1
Injury, poisoning and procedural complications			
Incision site pain			
subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	6	0	4
Joint sprain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	2 / 52 (3.85%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	2	1	0
Congenital, familial and genetic disorders			

Becker's muscular dystrophy			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	8	0	5
Atrial flutter			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	3	0	3
Bradycardia			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	6	0	3
Oedema due to cardiac disease			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	5	0	4
Mitral valve incompetence			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	3	0	2
Palpitations			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	6 / 46 (13.04%)
occurrences (all)	3	0	7
Pericardial effusion			
subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	6 / 46 (13.04%)
occurrences (all)	5	0	7
Pulmonary oedema			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences (all)	3	0	1
Right ventricular dysfunction			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	4	0	3
Tricuspid valve incompetence			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	3	0	2
Arrhythmia			

subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	3 / 52 (5.77%)	1 / 6 (16.67%)	1 / 46 (2.17%)
occurrences (all)	3	3	1
Dizziness			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	6	0	3
Headache			
subjects affected / exposed	11 / 52 (21.15%)	1 / 6 (16.67%)	13 / 46 (28.26%)
occurrences (all)	16	1	15
Paraesthesia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	5	0	3
Hypoaesthesia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	1	0	3
Tremor			
subjects affected / exposed	23 / 52 (44.23%)	1 / 6 (16.67%)	13 / 46 (28.26%)
occurrences (all)	28	1	14
Syncope			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	1 / 46 (2.17%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Aneamia			
subjects affected / exposed	18 / 52 (34.62%)	2 / 6 (33.33%)	15 / 46 (32.61%)
occurrences (all)	18	3	16
Leukocytosis			
subjects affected / exposed	9 / 52 (17.31%)	0 / 6 (0.00%)	9 / 46 (19.57%)
occurrences (all)	10	0	9
Leukopenia			
subjects affected / exposed	12 / 52 (23.08%)	0 / 6 (0.00%)	9 / 46 (19.57%)
occurrences (all)	15	0	9
Thrombocytopenia			

subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences (all)	7	0	1
Neutropenia			
subjects affected / exposed	2 / 52 (3.85%)	1 / 6 (16.67%)	2 / 46 (4.35%)
occurrences (all)	2	1	4
Eye disorders			
Amblyopia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	4	0	3
Abdominal pain			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	5 / 46 (10.87%)
occurrences (all)	6	0	5
Abdominal pain upper			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	3	0	2
Diarrhoea			
subjects affected / exposed	26 / 52 (50.00%)	1 / 6 (16.67%)	8 / 46 (17.39%)
occurrences (all)	36	1	10
Constipation			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	13 / 46 (28.26%)
occurrences (all)	7	0	13
Dysphagia			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	5	0	0
Gingival hyperplasia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	4
Mouth ulceration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Nausea			

subjects affected / exposed	8 / 52 (15.38%)	0 / 6 (0.00%)	15 / 46 (32.61%)
occurrences (all)	9	0	24
Vomiting			
subjects affected / exposed	3 / 52 (5.77%)	1 / 6 (16.67%)	9 / 46 (19.57%)
occurrences (all)	4	2	9
Gastritis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences (all)	2	0	1
Gingival hypertrophy			
subjects affected / exposed	1 / 52 (1.92%)	3 / 6 (50.00%)	1 / 46 (2.17%)
occurrences (all)	1	3	1
Tooth discolouration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	2 / 46 (4.35%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	6 / 46 (13.04%)
occurrences (all)	4	0	7
Hypertrichosis			
subjects affected / exposed	1 / 52 (1.92%)	3 / 6 (50.00%)	4 / 46 (8.70%)
occurrences (all)	1	3	4
Rash			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	3	0	4
Skin lesion			
subjects affected / exposed	7 / 52 (13.46%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	7	0	2
Skin ulcer			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	4	0	0
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	11 / 52 (21.15%)	0 / 6 (0.00%)	12 / 46 (26.09%)
occurrences (all)	14	0	13
Renal failure acute			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	4	0	4
Renal failure chronic			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Renal impairment			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	5 / 46 (10.87%)
occurrences (all)	3	0	5
Back pain			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	5 / 46 (10.87%)
occurrences (all)	4	0	5
Muscle spasms			
subjects affected / exposed	8 / 52 (15.38%)	0 / 6 (0.00%)	8 / 46 (17.39%)
occurrences (all)	8	0	8
Musculoskeletal chest pain			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	2	0	3
Musculoskeletal pain			
subjects affected / exposed	7 / 52 (13.46%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	7	0	2
Myalgia			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	6 / 46 (13.04%)
occurrences (all)	5	0	7
Pain in extremity			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	6	0	3
Infections and infestations			

Bronchitis			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	5	0	2
Diverticulitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Influenza			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	1	0	4
Nasopharyngitis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	6 / 46 (13.04%)
occurrences (all)	3	0	7
Pneumonia			
subjects affected / exposed	6 / 52 (11.54%)	1 / 6 (16.67%)	2 / 46 (4.35%)
occurrences (all)	7	1	2
Sinusitis			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	3	0	2
Staphylococcal infection			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	4	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 52 (7.69%)	2 / 6 (33.33%)	6 / 46 (13.04%)
occurrences (all)	4	2	6
Urinary tract infection			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	7	0	2
Adenovirus infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Clostridial infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	2
Gastroenteritis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0

Lower respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	0	0	2
Oral herpes			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	1 / 46 (2.17%)
occurrences (all)	1	1	1
Otitis media			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	1	1	0
Viral upper repiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Wound infection pseudomonas			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 6 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	2 / 46 (4.35%)
occurrences (all)	3	0	2
Diabetes mellitus			
subjects affected / exposed	6 / 52 (11.54%)	1 / 6 (16.67%)	11 / 46 (23.91%)
occurrences (all)	6	1	12
Fluid overload			
subjects affected / exposed	7 / 52 (13.46%)	0 / 6 (0.00%)	10 / 46 (21.74%)
occurrences (all)	8	0	17
Gout			

subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	5 / 46 (10.87%)
occurrences (all)	2	0	5
Hyperglycaemia			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	3 / 46 (6.52%)
occurrences (all)	6	0	3
Hyperkalaemia			
subjects affected / exposed	5 / 52 (9.62%)	2 / 6 (33.33%)	7 / 46 (15.22%)
occurrences (all)	6	2	7
Hyperlipidaemia			
subjects affected / exposed	5 / 52 (9.62%)	1 / 6 (16.67%)	8 / 46 (17.39%)
occurrences (all)	6	1	10
Hypoglycaemia			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	8	0	4
Hypokalaemia			
subjects affected / exposed	8 / 52 (15.38%)	2 / 6 (33.33%)	6 / 46 (13.04%)
occurrences (all)	8	2	7
Hypomagnesaemia			
subjects affected / exposed	13 / 52 (25.00%)	2 / 6 (33.33%)	4 / 46 (8.70%)
occurrences (all)	14	2	4
Hypovolaemia			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	4 / 46 (8.70%)
occurrences (all)	7	0	4
Fluid retention			
subjects affected / exposed	2 / 52 (3.85%)	1 / 6 (16.67%)	0 / 46 (0.00%)
occurrences (all)	2	1	0

Non-serious adverse events	Tacrolimus – Pediatric		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Hypotension			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Removal of foreign body			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hyperthermia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Oedema Peripheral			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Immune system disorders			

Transplant rejection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pneumothorax			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Aspiration			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory distress			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Insomnia			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Cardiac murmur			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Cytomegalovirus antigen positive			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Epstein-Barr virus antibody positive			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Incision site pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Joint sprain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Becker's muscular dystrophy			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Atrial flutter			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Bradycardia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Oedema due to cardiac disease			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Mitral valve incompetence			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pericardial effusion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pulmonary oedema			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Right ventricular dysfunction			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Tricuspid valve incompetence			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Arrhythmia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Aneamia			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Leukocytosis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Eye disorders			
Amblyopia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dysphagia			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Gingival hyperplasia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Gingival hypertrophy			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Tooth discolouration			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypertrichosis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Rash			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Skin lesion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Skin ulcer			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Renal failure acute			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Renal failure chronic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Renal impairment			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Diverticulitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Staphylococcal infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		

Adenovirus infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Clostridial infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Oral herpes subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Otitis media subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Respiratory syncytial virus infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Tooth abscess subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Viral upper repiratory tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Wound infection pseudomonas subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Metabolism and nutrition disorders Dyslipidaemia			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Fluid overload			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Gout			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hyperlipidaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Hypovolaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Fluid retention			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

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