Clinical trial results:
A Phase 2, Parallel Group, Randomized, Multicenter, Open-label Study to Compare the Pharmacokinetics of Tacrolimus in De Novo Pediatric Allograft Recipients Treated with an Advagraf® or Prograf® Based Immunosuppressive Regimen, Including a Long-term Follow-up

Summary

EudraCT number	2011-000078-80
Trial protocol	AT CZ BE PL IT FR
Global end of trial date	21 April 2021

Results information

Result version number	v2 (current)
This version publication date	05 November 2021
First version publication date	13 November 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	PMR-EC-1207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01614665
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe, Ltd
Sponsor organisation address	2000 Hillswood Drive, Chertsey, United Kingdom, KT16 0RS
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe, Ltd, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe, Ltd, 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?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 April 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the systemic exposure (area under the plasma concentration-time curve from time 0 to time 24 hours [AUC24]) of tacrolimus for tacrolimus prolonged release (Advagraf) vs tacrolimus (Prograf) after the first dose and following repeated administration in pediatric patients undergoing primary heart, kidney or liver transplantation.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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:

This study is composed of 3 parts: Part A (pharmacokinetics), Part B (long-term follow-up) and Part C (continuation of long-term follow-up until participants discontinued treatment or received the approved treatment). Basiliximab, mycophenolate mofetil (MMF) and corticosteroids could have been administered as concomitant immunosuppressive treatment. Basiliximab and MMF were administered according to current accepted local and institutional clinical practice. Corticosteroids were administered following a predetermined schedule in Part A, and then in Part B or C followed the routine practice of the center.

Evidence for comparator: -

Actual start date of recruitment	03 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Poland: 7
Worldwide total number of subjects	44
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	24
Adolescents (12-17 years)	20
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part C was conducted only to provide Advagraf to pediatric subjects without interruption until they withdrew from the study or reached age 18 years which ever occurred first as Advagraf is not yet approved for pediatric use. Only safety data was collected in Part C, efficacy evaluation was not performed as this was not a study objective.

Pre-assignment

Screening details:

Eligible pediatric subjects(<16 years of age) undergoing primary heart, kidney or liver transplantation(de novo allograft) were enrolled and were randomized to either tacrolimus/tacrolimus prolonged release on 1:1 basis stratified by organ and center. Study conducted in-France(Part A,B), and Czech Republic, Italy, Poland, UK(Part A, B, C).

Period 1

Period 1 title	Part A: Pharmacokinetics
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tacrolimus (Part A)

Arm description:

Subjects received an initial dose of tacrolimus orally or via nasogastric tube on day 1, and subsequently twice daily for up to 4 weeks in Part A of the study.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Prograf
Pharmaceutical forms	Capsule, hard
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Subjects received an initial total daily dose of tacrolimus depending on the type of organ transplant (heart = 0.075 mg/kg; liver/kidney = 0.3 mg/kg), given orally (or via nasogastric tube for liver transplant recipients) in 2 doses in the morning and the evening. The first dose was administered in the morning within days of skin closure (heart = 4 days; liver = 2 days; kidney = within 24 hours following reperfusion). Subsequent tacrolimus doses were taken orally twice a day in the morning and evening and were adjusted on the basis of clinical evidence of efficacy, occurrence of adverse events and observing the recommended whole blood trough level ranges (Day 1 through 21 = 10 to 20 ng/mL; Day 22 through 365 = 5 to 15 ng/mL).

Arm title	Tacrolimus Prolonged Release (Part A)

Arm description:

Subjects received an initial dose of tacrolimus prolonged release orally or via nasogastric tube on day 1, and subsequently once daily for up to 4 weeks in Part A of the study.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus prolonged release
Investigational medicinal product code	
Other name	Advagraf, Astagraf XL, Graceptor, Prograf XL
Pharmaceutical forms	Capsule, hard
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Subjects received an initial total daily dose of tacrolimus prolonged release depending on the type of organ transplant (heart = 0.075 mg/kg; liver/kidney = 0.3 mg/kg), given orally (or via nasogastric tube

for liver transplant recipients) in 1 dose. The first dose was administered in the morning within days of skin closure (heart = 4 days; liver = 2 days; kidney = within 24 hours following reperfusion). Subsequent tacrolimus prolonged release doses were taken orally once a day in the morning and were adjusted on the basis of clinical evidence of efficacy, occurrence of adverse events and observing the recommended whole blood trough level ranges (Day 1 through 21 = 10 to 20 ng/mL; Day 22 through 365 = 5 to 15 ng/mL).

Number of subjects in period 1	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)
Started	24	20
Treated with Study Drug	24	20
Completed	23	20
Not completed	1	0
Withdrawal of Consent	1	-

Period 2

Period 2 title	Part B: Long-Term Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tacrolimus (Part B)

Arm description:

After Part A, subjects continued to receive tacrolimus twice daily for up to 48 weeks in Part B of the study.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Prograf
Pharmaceutical forms	Capsule, hard
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Subjects received an initial total daily dose of tacrolimus depending on the type of organ transplant (heart = 0.075 mg/kg; liver/kidney = 0.3 mg/kg), given orally (or via nasogastric tube for liver transplant recipients) in 2 doses in the morning and the evening. The first dose was administered in the morning within days of skin closure (heart = 4 days; liver = 2 days; kidney = within 24 hours following reperfusion). Subsequent tacrolimus doses were taken orally twice a day in the morning and evening and were adjusted on the basis of clinical evidence of efficacy, occurrence of adverse events and observing the recommended whole blood trough level ranges (Day 1 through 21 = 10 to 20 ng/mL; Day 22 through 365 = 5 to 15 ng/mL).

Arm title	Tacrolimus Prolonged Release (Part B)

Arm description:

After Part A, subjects continued to receive tacrolimus prolonged release twice daily for up to 48 weeks in

Part B of the study.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus prolonged release
Investigational medicinal product code	
Other name	Advagraf, Astagraf XL, Graceptor, Prograf XL
Pharmaceutical forms	Capsule, hard
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Subjects received an initial total daily dose of tacrolimus prolonged release depending on the type of organ transplant (heart = 0.075 mg/kg; liver/kidney = 0.3 mg/kg), given orally (or via nasogastric tube for liver transplant recipients) in 1 dose. The first dose was administered in the morning within days of skin closure (heart = 4 days; liver = 2 days; kidney = within 24 hours following reperfusion). Subsequent tacrolimus prolonged release doses were taken orally once a day in the morning and were adjusted on the basis of clinical evidence of efficacy, occurrence of adverse events and observing the recommended whole blood trough level ranges (Day 1 through 21 = 10 to 20 ng/mL; Day 22 through 365 = 5 to 15 ng/mL).

Number of subjects in period 2	Tacrolimus (Part B)	Tacrolimus Prolonged Release (Part B)
Started	23	20
Treated with Study Drug	23	20
Completed	21	20
Not completed	2	0
Noncompliance with scheduled visits	1	-
Adverse Event	1	-

Period 3

Period 3 title	Part C
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tacrolimus Prolonged Release (Part C)

Arm description:

After Part B, eligible subjects continued to receive tacrolimus prolonged release capsule per investigator's opinion until tacrolimus prolonged release became available to the subjects for commercial use, or the subjects discontinued, or subjects reached to 18 years of age whichever was the earliest (up to 3 years 11 months).

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Advagraf
Pharmaceutical forms	Capsule, hard
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Subjects received an initial total daily dose of tacrolimus prolonged release depending on the type of organ transplant (heart = 0.075 mg/kg; liver/kidney = 0.3 mg/kg), given orally (or via nasogastric tube for liver transplant recipients) in 1 dose. The first dose was administered in the morning within days of skin closure (heart = 4 days; liver = 2 days; kidney = within 24 hours following reperfusion). Subsequent tacrolimus prolonged release doses were taken orally once a day in the morning and were adjusted on the basis of occurrence of adverse events and blood trough level ranges on plus/minus 30 days of clinical visits.

Number of subjects in period 3[1]	Tacrolimus Prolonged Release (Part C)
Started	12
Completed	6
Not completed	6
Death	1
Withdrawal by Subject	2
Miscellaneous	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only eligible subjects from Part B entered Part C.

Baseline characteristics

Reporting groups	
Reporting group title	Tacrolimus (Part A)
Reporting group description:	
Subjects received an initial dose of tacrolimus orally or via nasogastric tube on day 1, and subsequently twice daily for up to 4 weeks in Part A of the study.	
Reporting group title	Tacrolimus Prolonged Release (Part A)
Reporting group description:	
Subjects received an initial dose of tacrolimus prolonged release orally or via nasogastric tube on day 1, and subsequently once daily for up to 4 weeks in Part A of the study.	

Reporting group values	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)	Total
Number of subjects	24	20	44
Age categorical Units: Subjects			
≥ 0 days to ≤ 27 days (newborn)	0	0	0
≥ 28 days to ≤ 23 months (infants and toddlers)	0	0	0
≥ 2 years to ≤ 11 years (children)	13	11	24
≥ 12 years to ≤ 17 years (adolescents)	11	9	20
Age continuous Units: years			
arithmetic mean	10.25	11.10	
standard deviation	± 3.21	± 3.02	-
Gender categorical Units:			
Male	17	16	33
Female	7	4	11
Type of Organ Transplant Units: Subjects			
Heart	4	3	7
Kidney	12	13	25
Liver	8	4	12

End points

End points reporting groups

Reporting group title	Tacrolimus (Part A)
Reporting group description:	
Subjects received an initial dose of tacrolimus orally or via nasogastric tube on day 1, and subsequently twice daily for up to 4 weeks in Part A of the study.	
Reporting group title	Tacrolimus Prolonged Release (Part A)
Reporting group description:	
Subjects received an initial dose of tacrolimus prolonged release orally or via nasogastric tube on day 1, and subsequently once daily for up to 4 weeks in Part A of the study.	
Reporting group title	Tacrolimus (Part B)
Reporting group description:	
After Part A, subjects continued to receive tacrolimus twice daily for up to 48 weeks in Part B of the study.	
Reporting group title	Tacrolimus Prolonged Release (Part B)
Reporting group description:	
After Part A, subjects continued to receive tacrolimus prolonged release twice daily for up to 48 weeks in Part B of the study.	
Reporting group title	Tacrolimus Prolonged Release (Part C)
Reporting group description:	
After Part B, eligible subjects continued to receive tacrolimus prolonged release capsule per investigator's opinion until tacrolimus prolonged release became available to the subjects for commercial use, or the subjects discontinued, or subjects reached to 18 years of age whichever was the earliest (up to 3 years 11 months).	
Subject analysis set title	Tacrolimus (Part A+B)
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received tacrolimus twice daily starting from day 1 for 4 weeks for in Part A, and continued to receive tacrolimus twice daily up to end of Part B of the study.	
Subject analysis set title	Tacrolimus prolonged release (Part A+B)
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received tacrolimus prolonged release once daily starting from day 1 for 4 weeks for in Part A, and continued to receive tacrolimus prolonged release once daily up to end of Part B of the study.	

Primary: Area Under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours (AUC0-24h) for Tacrolimus

End point title	Area Under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours (AUC0-24h) for Tacrolimus
End point description:	
The analysis population was the Pharmacokinetic Set (PKAS), which included all subjects who received at least one dose of study drug and who provided 3 complete pharmacokinetic (PK) profiles.	
End point type	Primary
End point timeframe:	
Days 1, 7 and 28 at predose, 1, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose	

End point values	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Day 1	224.1438 (± 55.4)	157.3656 (± 63.4)		
Day 7	295.4154 (± 35.9)	292.4430 (± 36.0)		
Day 28	260.0736 (± 38.4)	268.9836 (± 36.7)		

Statistical analyses

Statistical analysis title	AUC0-24h Comparison on Day 1

Statistical analysis description:

The comparison of AUC0-24h between tacrolimus and tacrolmus prolonged release was assessed using an analysis of covariance (ANCOVA) model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus Prolonged Release (Part A) v Tacrolimus (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least squares (LS) mean ratio
Point estimate	66.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	46.39
upper limit	94.84

Statistical analysis title	AUC0-24h Comparison on Day 28

Statistical analysis description:

The comparison of AUC0-24h between tacrolimus and tacrolmus prolonged release was assessed using an ANCOVA model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other

Parameter estimate	Geometric LS mean ratio
Point estimate	99.91
Confidence interval	
level	90 %
sides	2-sided
lower limit	80.64
upper limit	123.78

Statistical analysis title	AUC0-24h Comparison on Day 7

Statistical analysis description:

The comparison of AUC0-24h between tacrolimus and tacrolmus prolonged release was assessed using an ANCOVA model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric LS mean ratio
Point estimate	92.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	71.22
upper limit	120.09

Primary: Number of Subjects with Adverse Events

End point title	Number of Subjects with Adverse Events[1]

End point description:

Safety was assessed by adverse events (AEs), which included abnormalities identified during a medical test (e.g. laboratory tests, vital signs, electrocardiogram, etc.) if the abnormality induced clinical signs or symptoms, needed active intervention, interruption or discontinuation of study medication or was clinically significant. A serious AE (SAE) was an event resulting in death, persistent or significant disability/incapacity or congenital anomaly or birth defect, was life-threatening, required or prolonged hospitalization or was considered medically important. The analysis population was the Full Analysis Set (FAS), which consisted of all subjects who received at least one dose of any of the study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to 7 days after last dose of study drug in Part B (up to 53 weeks), From first dose of study in Part C up to 7 days after last dose in Part C (up to 3 years 11 months)

Notes:

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

End point values	Tacrolimus Prolonged Release (Part C)	Tacrolimus (Part A+B)	Tacrolimus prolonged release (Part A+B)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	24	20	
Units: subjects				
number (not applicable)				
TEAEs	10	23	19	
Drug-related AEs	5	15	14	
Deaths	1	0	0	
SAEs	8	15	13	
Drug-related SAEs	4	9	10	
Deaths Resulting from AEs	0	0	0	
AEs Leading to Discontinuation of Study Drug	0	1	0	
Drug-related AEs Leading to Discont. of Study Drug	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Tacrolimus

End point title	Maximum Concentration (Cmax) of Tacrolimus

End point description:

The analysis population was the PKAS. This PK parameter was not assessed in the evening for the tacrolimus prolonged release arm as the subjects received only one dose in the morning, and therefore is denoted as "99999." One subject had an assessment in the evening of day 1, and data available are included below.

End point type	Secondary

End point timeframe:

Days 1, 7 and 28 at predose, 1, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose

End point values	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15[2]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: Morning	14.7228 (± 68.7)	12.7344 (± 67.9)		
Day 1: Evening	17.3022 (± 67.0)	4.0000 (± 99999)		
Day 7: Morning	20.9616 (± 52.3)	26.7438 (± 50.9)		
Day 7: Evening	15.5052 (± 57.0)	99999 (± 99999)		

Day 28: Morning	22.9368 (± 54.9)	21.3462 (± 32.0)		
Day 28: Evening	12.6120 (± 34.2)	99999 (± 99999)		

Notes:

[2] - The number of subjects for day 1=14.

Statistical analyses

Statistical analysis title	Cmax Comparison on Day 1

Statistical analysis description:

The comparison of Cmax between tacrolimus and tacrolmus prolonged release was assessed using an ANCOVA model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric LS mean ratio
Point estimate	77.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	52.64
upper limit	113.49

Statistical analysis title	Cmax Comparison on Day 7

Statistical analysis description:

The comparison of Cmax between tacrolimus and tacrolmus prolonged release was assessed using an ANCOVA model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric LS mean ratio
Point estimate	120.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.32
upper limit	165.83

Statistical analysis title	Cmax Comparison on Day 28

Statistical analysis description:

The comparison of Cmax between tacrolimus and tacrolmus prolonged release was assessed using an ANCOVA model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric LS mean ratio
Point estimate	92.16
Confidence interval	
level	90 %
sides	2-sided
lower limit	72.33
upper limit	117.42

Secondary: Time to Attain Maximum Concentration (tmax) of Tacrolimus

End point title	Time to Attain Maximum Concentration (tmax) of Tacrolimus

End point description:

The analysis population was the PKAS. This PK parameter was not assessed in the evening for the tacrolimus prolonged release arm as the subjects received only one dose in the morning, and therefore is denoted as "99999." One subject had an assessment in the evening of day 1, and data available are included below.

End point type	Secondary

End point timeframe:

Days 1, 7 and 28 at predose, 1, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose

End point values	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15[3]		
Units: hours				
median (full range (min-max))				
Day 1: Morning	1.9998 (0.000 to 11.751)	3.9498 (0.984 to 23.001)		
Day 1: Evening	1.9998 (0.966 to 11.250)	6.0000 (6.000 to 6.000)		
Day 7: Morning	1.0086 (0.951 to 6.051)	1.9998 (0.966 to 13.032)		
Day 7: Evening	3.9582 (0.000 to 12.018)	99999 (99999 to 999999)		
Day 28: Morning	1.0002 (0.933 to 3.984)	1.9500 (0.918 to 6.000)		
Day 28: Evening	3.9414 (0.999 to 12.000)	99999 (99999 to 99999)		

Notes:

[3] - The number of subjects for day 1=14.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (C12) for Tacrolimus

End point title	Trough Concentration (C12) for Tacrolimus[4]

End point description:

The analysis population was the PKAS.

End point type	Secondary

End point timeframe:

Days 1, 7 and 28, 12 hours after dosing

Notes:

[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: Combined outcome measure data is presented for tacrolimus and tacrolimus prolonged release by using subject analysis set for Parts A and B.

End point values	Tacrolimus (Part A)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1	5.2224 (± 61.8)			
Day 7	8.7840 (± 45.0)			
Day 28	7.4322 (± 37.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (C24) for Tacrolimus

End point title	Trough Concentration (C24) for Tacrolimus

End point description:

The analysis population was the PKAS.

End point type	Secondary

End point timeframe:

Days 1, 7 and 28, 24 hours after dosing

End point values	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[5]	15		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1	6.8154 (± 58.5)	5.0736 (± 63.9)		
Day 7	9.0744 (± 30.5)	7.7442 (± 46.3)		
Day 28	7.9188 (± 38.9)	7.0506 (± 45.6)		

Notes:

[5] - The number of subjects for day 28=17.

Statistical analyses

Statistical analysis title	C24 Comparison on Day 1

Statistical analysis description:

The comparison of C24 between tacrolimus and tacrolmus prolonged release was assessed using an ANCOVA model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric LS mean ratio
Point estimate	66.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	44.63
upper limit	98.46

Statistical analysis title	C24 Comparison on Day 7

Statistical analysis description:

The comparison of C24 between tacrolimus and tacrolmus prolonged release was assessed using an ANCOVA model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric LS mean ratio

Point estimate	82.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	63.36
upper limit	106.65

Statistical analysis title	C24 Comparison on Day 28

Statistical analysis description:

The comparison of C24 between tacrolimus and tacrolmus prolonged release was assessed using an ANCOVA model on log-transformed pharmacokinetic parameters with treatment and organ transplant as fixed effects and age at baseline as continuous covariate. The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolmus prolonged release and its 90% CI are back-transformed to the raw scale and expressed as percentages.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric LS mean ratio
Point estimate	90.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	69.62
upper limit	118.64

Secondary: Correlation between AUC24 & C24

End point title	Correlation between AUC24 & C24

End point description:

The analysis population was the PKAS. Only subjects with available C24 and AUC24 at each visit are included in the analysis.

End point type	Secondary

End point timeframe:

Days 1, 7 and 28 at predose, 1, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose

End point values	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[6]	15		
Units: pearson correlation coefficient				
number (not applicable)				
Day 1	0.82	0.87		
Day 7	0.87	0.72		
Day 28	0.88	0.87		

Notes:

[6] - The number of subjects for day 28=17.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Acute Rejections

End point title	Number of Subjects with Acute Rejections

End point description:

Rejection episodes/acute rejections were indicated by clinical and/or laboratory signs, and were classified according to their rejection specific treatment: •Spontaneously Resolving Acute Rejection: not treated with new or increased corticosteroid medication, antibodies or any other medication and resolved, irrespective of any tacrolimus dose changes; •Corticosteroid Sensitive Acute Rejection: treated with new or increased corticosteroid medication only and which has resolved, irrespective of any tacrolimus dose changes; •Corticosteroid Resistant Acute Rejection: did not resolve following treatment with corticosteroids; - Resolved with further treatment: any acute rejection with an end date AND a treatment other than corticosteroid used; - Unresolved with further treatment: any acute rejection with no end date AND a treatment other than corticosteroid used; - Unresolved with no further treatment: any acute rejection with no end date AND ONLY corticosteroid treatment was used. FAS.

End point type	Secondary

End point timeframe:

Up to 7 years 5 months

End point values	Tacrolimus Prolonged Release (Part C)	Tacrolimus (Part A+B)	Tacrolimus prolonged release (Part A+B)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	24	20	
Units: participants				
number (not applicable)				
1. Any Acute Rejections	3	7	2	
1.a. Spontaneously Resolving Acute Rejection	0	1	0	
1.b. Corticosteroid Sensitive Acute Rejection	0	6	2	
1.c. Corticosteroid Resistant Acute Rejection	0	0	0	
1.c.1 Resolved with further treatment	3	0	0	
1.c.2 Unresolved with further treatment	0	0	0	
1.c.3 Unresolved with no further treatment	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Biopsy-proven Acute Rejection Episodes (BPARs)

End point title	Number of Subjects with Biopsy-proven Acute Rejection Episodes (BPARs)

End point description:

BPAR episodes were defined as acute rejection episodes confirmed by biopsy, and were classified according to their rejection specific treatment: •Spontaneously Resolving Acute Rejection: not treated with new or increased corticosteroid medication, antibodies or any other medication and resolved, irrespective of any tacrolimus dose changes; •Corticosteroid Sensitive Acute Rejection: treated with new or increased corticosteroid medication only and which has resolved, irrespective of any tacrolimus dose changes; •Corticosteroid Resistant Acute Rejection: did not resolve following treatment with corticosteroids; - Resolved with further treatment: any acute rejection with an end date AND a treatment other than corticosteroid used; - Unresolved with further treatment: any acute rejection with no end date AND a treatment other than corticosteroid used; - Unresolved with no further treatment: any acute rejection with no end date AND ONLY corticosteroid treatment used. FAS.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Tacrolimus (Part A+B)	Tacrolimus prolonged release (Part A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	20		
Units: subjects				
number (not applicable)				
1. Biopsy proven acute rejections	4	1		
1.a. Spontaneously Resolving Acute Rejection	1	0		
1.b. Corticosteroid Sensitive Acute Rejection	3	1		
1.c. Corticosteroid Resistant Acute Rejection	0	0		
1.c.1 Resolved with further treatment	0	0		
1.c.2 Unresolved with further treatment	0	0		
1.c.3 Unresolved with no further treatment	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of Biopsy Proven Acute Rejection Episodes

End point title	Severity of Biopsy Proven Acute Rejection Episodes

End point description:

The severity of BPARs was categorized with specific criteria by organ: For kidney transplant participants, according to Banff '97 Diagnostic categories for renal allograft biopsies – Banff '07 update (C4d deposition, Acute antibody-mediated rejection I, II, and III, Acute T cell mediated rejection IA, IB, IIA, IIB and III); for liver transplant participants, according to 1997 Banff Schema for Grading of Liver Allograft Rejection - Rejection Activity Index (mild, moderate, severe or indeterminate/borderline); for heart, according to Standardized Nomenclature of the International Society of Heart and Lung Transplantation - Standardised Cardiac Biopsy Grading: Acute Cellular Rejection 2004 (mild, moderate,

severe). N is the number of subjects analyzed by type of organ transplant in each arm. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Tacrolimus (Part A+B)	Tacrolimus prolonged release (Part A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	20		
Units: subjects				
number (not applicable)				
Kidney [N=12, 13]: C4d deposition	0	0		
Kidney [N=12, 13]: Antibody-mediated rejection I	0	0		
Kidney [N=12, 13]: Antibody-mediated rejection II	0	0		
Kidney [N=12, 13]: Antibody-mediated rejection III	0	0		
Kidney [N=12, 13]: T cell mediated rejection IA	0	0		
Kidney [N=12, 13]: T cell mediated rejection IB	0	0		
Kidney [N=12, 13]: T cell mediated rejection IIA	0	0		
Kidney [N=12, 13]: T cell mediated rejection IIB	0	0		
Kidney [N=12, 13]: T cell mediated rejection III	0	0		
Liver [N=8, 4]: Mild	2	1		
Liver [N=8, 4]: Moderate	1	0		
Liver [N=8, 4]: Severe	1	0		
Liver [N=8, 4]: Indeterminate or borderline	0	0		
Heart [N=4, 3]: Mild	0	0		
Heart [N=4, 3]: Moderate	0	0		
Heart [N=4, 3]: Severe	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Survival

End point title	Patient Survival

End point description:

Patient survival was defined as the time from first dose of study drug to the date of death from any cause. Since no subjects died during the study, survival analysis was not conducted.

End point type	Secondary

End point timeframe:

End point values	Tacrolimus (Part A+B)	Tacrolimus prolonged release (Part A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[7]	0[8]		
Units: days				
number (confidence interval 95%)	(to)	(to)		

Notes:

[7] - There were no deaths.

[8] - There were no deaths.

Statistical analyses

No statistical analyses for this end point

Secondary: Graft Survival

End point title	Graft Survival

End point description:

Graft survival was defined as the time from the first dose of study drug to graft loss. Graft loss was defined as retransplantation, nephrectomy (in case of kidney transplantation), death or dialysis (in case of kidney transplantation) ongoing at end of study or at discontinuation, unless superseded by follow-up information. Since no subjects experienced graft loss during the study, survival analysis was not conducted.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Tacrolimus (Part A+B)	Tacrolimus prolonged release (Part A+B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[9]	0[10]		
Units: days				
number (confidence interval 95%)	(to)	(to)		

Notes:

[9] - There were no graft losses.

[10] - There were no graft losses.

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy Failure

End point title	Efficacy Failure

End point description:

Efficacy failure was defined as the composite of the following: death, graft loss, BPAR and unknown outcome. A subject was considered to have an unknown outcome if he/she did not have the event of interest (death, graft loss, BPAR) or did not have a study assessment prior to day 335. Three subjects in the tacolimus group had efficacy failure due to an unknown outcome as these 3 subjects discontinued early from the study. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

Up to 7 years 5 months

End point values	Tacrolimus Prolonged Release (Part C)	Tacrolimus (Part A+B)	Tacrolimus prolonged release (Part A+B)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	24	20	
Units: subjects				
number (not applicable)				
Graft loss	0	0	0	
BPAR	0	4	1	
Death	1	0	0	
Unknown	0	3	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 7 days after last dose of study drug in Part B (up to 53 weeks), From first dose of study in Part C up to 7 days after last dose in Part C (up to 3 years 11 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Tacrolimus (Part A + B)

Reporting group description:

Subjects received tacrolimus twice daily starting from day 1 for 4 weeks for in Part A, and continued to receive tacrolimus twice daily up to end of Part B of the study.

Reporting group title	Tacrolimus Prolonged Release (Part C)

Reporting group description:

After Part B, eligible subjects continued to receive tacrolimus prolonged release capsule per investigator's opinion until tacrolimus prolonged release became available to the subjects for commercial use, or the subjects discontinued, or subjects reached to age of 18 years, whichever was the earliest (up to 3 years 11 months).

Reporting group title	Tacrolimus prolonged release (Part A + B)

Reporting group description:

Subjects received tacrolimus prolonged release once daily starting from day 1 for 4 weeks for in Part A, and continued to receive tacrolimus prolonged release once daily up to end of Part B of the study.

Serious adverse events	Tacrolimus (Part A + B)	Tacrolimus Prolonged Release (Part C)	Tacrolimus prolonged release (Part A + B)
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 24 (62.50%)	7 / 12 (58.33%)	13 / 20 (65.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Device connection issue			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Incision site pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Transplant failure			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	2 / 24 (8.33%)	3 / 12 (25.00%)	5 / 20 (25.00%)
occurrences causally related to treatment / all	1 / 3	1 / 3	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Brain scan abnormal			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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

Blood phosphorus decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Histology abnormal			
subjects affected / exposed	2 / 24 (8.33%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Transaminases increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (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
Congenital, familial and genetic disorders			
Congenital ectodermal dysplasia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Febrile neutropenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Thrombocytopenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	0 / 24 (0.00%)	2 / 12 (16.67%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenoidal hypertrophy			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Lethargy			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)

occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reversible posterior leukoencephalopathy syndrome			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Gastritis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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			
Bile duct stenosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary fistula			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Focal segmental glomerulosclerosis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
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 impairment			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Residual urine			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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			
Bronchitis bacterial			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (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

Cytomegalovirus viraemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis adenovirus			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Gastroenteritis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (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
Gastroenteritis sapovirus			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Oral candidiasis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
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			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyomavirus-associated nephropathy			

subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (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
Septic shock			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Tonsillitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 20 (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
Urinary tract infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (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
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tacrolimus (Part A + B)	Tacrolimus Prolonged Release (Part C)	Tacrolimus prolonged release (Part A + B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 24 (91.67%)	6 / 12 (50.00%)	19 / 20 (95.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 24 (37.50%)	0 / 12 (0.00%)	6 / 20 (30.00%)
occurrences (all)	9	0	6

Peripheral coldness			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Post procedural drainage			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	4	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papilloma			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Social circumstances			
Exposure to communicable disease			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Bloody discharge			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Pyrexia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	3 / 20 (15.00%)
occurrences (all)	4	0	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 24 (4.17%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Hallucination			

subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Restlessness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Complications of transplanted kidney			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Expired drug administered			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Drug dispensing error			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Joint dislocation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Wrist fracture			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	3 / 20 (15.00%)
occurrences (all)	3	0	4
Blood iron decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)

occurrences (all)	0	0	1
Blood magnesium decreased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Blood urea increased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	2
Blood phosphorus decreased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Body temperature increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Heart rate decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Immunosuppressant drug level decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Immunosuppressant drug level increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Oxygen saturation decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Urine output decreased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Weight increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

Pericardial effusion			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Tachycardia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	4 / 24 (16.67%)	0 / 12 (0.00%)	4 / 20 (20.00%)
occurrences (all)	4	0	11
Nasal congestion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Interstitial lung disease			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Pleural effusion			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	5	0	2
Sneezing			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Tonsillar hypertrophy			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	4 / 24 (16.67%)	0 / 12 (0.00%)	4 / 20 (20.00%)
occurrences (all)	6	0	5
Neutropenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	2
Leukopenia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	3	0	1
Thrombocytopenia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	3	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 24 (8.33%)	1 / 12 (8.33%)	4 / 20 (20.00%)
occurrences (all)	2	1	4
Paraesthesia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Reversible posterior leukoencephalopathy syndrome			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Visual impairment			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1

Abdominal pain			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	3	0	4
Aphthous stomatitis			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	4	0	1
Abdominal pain lower			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	11 / 24 (45.83%)	0 / 12 (0.00%)	11 / 20 (55.00%)
occurrences (all)	12	0	19
Constipation			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	3 / 20 (15.00%)
occurrences (all)	2	0	3
Dyspepsia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 12 (8.33%)	1 / 20 (5.00%)
occurrences (all)	3	1	1
Gastrointestinal pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Lip oedema			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	4 / 20 (20.00%)
occurrences (all)	4	0	4
Peritoneal effusion			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1

Vomiting			
subjects affected / exposed	5 / 24 (20.83%)	0 / 12 (0.00%)	5 / 20 (25.00%)
occurrences (all)	8	0	7
Renal and urinary disorders			
Detrusor sphincter dyssynergia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nocturia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Cholelithiasis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Cholestasis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Jaundice			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Night sweats			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	3
Muscle spasms			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Osteopenia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Anorexia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Glucose tolerance impaired			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)

occurrences (all)	2	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Hyperuricaemia			
subjects affected / exposed	2 / 24 (8.33%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Hyponatraemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Metabolic acidosis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 12 (8.33%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Hypophosphataemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Vitamin D deficiency			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Bronchitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Bronchopneumonia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Cytomegalovirus infection			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	3	0	2
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Epididymitis			

subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Epstein-Barr viraemia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Epstein-Barr virus infection			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Gastroenteritis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	2
Gastroenteritis viral			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	2 / 24 (8.33%)	1 / 12 (8.33%)	2 / 20 (10.00%)
occurrences (all)	2	1	2
Oral candidiasis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Oral herpes			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Pyelonephritis			

subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Respiratory tract infection viral			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Rubella			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	2 / 20 (10.00%)
occurrences (all)	3	0	3
Tonsillitis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 12 (8.33%)	1 / 20 (5.00%)
occurrences (all)	1	2	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 24 (16.67%)	0 / 12 (0.00%)	4 / 20 (20.00%)
occurrences (all)	4	0	6
Urinary tract infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 24 (12.50%)	0 / 12 (0.00%)	1 / 20 (5.00%)
occurrences (all)	4	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2011	This amendment was issued to change an inclusion criterion specific to heart transplant patients, to update the specifics regarding concomitant medications (antibody induction, mycophenolate mofetil [MMF], steroids) and prohibited concomitant medications, to change the emergency contact to clarify the safety reporting requirements.
21 October 2013	This amendment added the Part C extension to the study (particularly for Italy and Poland).
13 May 2014	This amendment added the Part C extension to the study (particularly for Czech Republic).
28 June 2016	This amendment added the Part C extension to the study for the United Kingdom.
05 May 2020	This amendment added for Part C to update the sponsor contact details, schedule of assessments. Country-specific amendments for Italy, Poland and the Czech Republic were also prepared.
06 May 2020	This amendment added for Part C to update the sponsor contact details, schedule of assessments. Country-specific amendment for UK was also prepared.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported