



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	

Results information

Result version number	v1
This version publication date	13 November 2017
First version publication date	13 November 2017

Trial information

Trial identification

Sponsor protocol code	PMR-EC-1207
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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	Interim
Date of interim/final analysis	11 May 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	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	Czech Republic: 10
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	44
EEA total number of subjects	44

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:

Children aged < 16 years of age were enrolled in sites in 5 countries: Czech Republic, France, Italy, Poland and UK for this 3-part study. Results reported in this disclosure include data from Part A and Part B of the study.

Pre-assignment

Screening details:

Pediatric participants undergoing primary heart, kidney or liver transplantation (de novo allograft) meeting the eligibility criteria were enrolled. Participants were randomized to treatment with either tacrolimus and tacrolimus prolonged release on a 1:1 basis stratified by organ and center.

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:

Participants 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:

Participants 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)
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Arm description:

Participants 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:

Participants 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 A)

Arm description:

After Part A, participants 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:

Participants 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)
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Arm description:

After Part A, participants continued to receive tacrolimus prolonged release once 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:

Participants 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 A)	Tacrolimus Prolonged Release (Part B)
Started	23	20
Treated with Study Drug	23	20
Completed	21	20
Not completed	2	0
Adverse Event	1	-
Noncompliance with scheduled visits	1	-

Baseline characteristics

Reporting groups

Reporting group title	Tacrolimus (Part A)
Reporting group description: Participants 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: Participants 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: Participants 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: Participants 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 A)
Reporting group description: After Part A, participants 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, participants continued to receive tacrolimus prolonged release once daily for up to 48 weeks in Part B of the study.	
Subject analysis set title	Tacrolimus (Part A+B)
Subject analysis set type	Full analysis
Subject analysis set description: Participants 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: Participants 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 participants 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 (\pm 35.9)	292.4430 (\pm 36.0)		
Day 28	260.0736 (\pm 38.4)	268.9836 (\pm 36.7)		

Statistical analyses

Statistical analysis title	AUC0-24h Comparison on Day 1
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Statistical analysis description:

The comparison of AUC0-24h between tacrolimus and tacrolimus 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 tacrolimus 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 7
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Statistical analysis description:

The comparison of AUC0-24h between tacrolimus and tacrolimus 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 tacrolimus 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

Statistical analysis title	AUC0-24h Comparison on Day 28
Statistical analysis description:	
The comparison of AUC0-24h between tacrolimus and tacrolimus 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 tacrolimus 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

Primary: Number of Participants with Adverse Events (Part A + B)

End point title	Number of Participants with Adverse Events (Part A + B) ^[1]
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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 participants who received at least one dose of any of the study drug.

End point type	Primary
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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)

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: There were no pre-determined hypothesis or other statistical analyses performed on the primary safety endpoint.

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: participants				
number (not applicable)				
AEs	23	19		
Drug-related AEs	15	14		
Deaths	0	0		
SAEs	15	13		
Drug-related SAEs	9	10		
Deaths Resulting from AEs	0	0		

AEs Leading to Discontinuation of Study Drug	1	0		
Drug-related AEs Leading to Discont. of Study Drug	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 participants received only one dose in the morning, and therefore is denoted as "99999." One participant 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 participants for day 1=14.

Statistical analyses

Statistical analysis title	Cmax Comparison on Day 1
Statistical analysis description: The comparison of Cmax between tacrolimus and tacrolimus 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 tacrolimus 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
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Statistical analysis description:

The comparison of Cmax between tacrolimus and tacrolimus 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 tacrolimus 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
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Statistical analysis description:

The comparison of Cmax between tacrolimus and tacrolimus 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 tacrolimus 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)
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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 participants received only one dose in the morning, and therefore is denoted as "99999." One participant 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 participants 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]
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End point description:

The analysis population was the PKAS.

End point type	Secondary
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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: This PK parameter only applies to the tacrolimus group, due to the frequency of the study drug administration.

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
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End point description:

The analysis population was the PKAS.

End point type	Secondary
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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 (\pm 30.5)	7.7442 (\pm 46.3)		
Day 28	7.9188 (\pm 38.9)	7.0506 (\pm 45.6)		

Notes:

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

Statistical analyses

Statistical analysis title	C24 Comparison on Day 1
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Statistical analysis description:

The comparison of C24 between tacrolimus and tacrolimus 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 tacrolimus 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
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Statistical analysis description:

The comparison of C24 between tacrolimus and tacrolimus 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 tacrolimus 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 tacrolimus 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 tacrolimus 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 participants 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 participants for day 28=17.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Acute Rejections

End point title	Number of Participants 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 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: participants				
number (not applicable)				
1. Any Acute Rejections	7	2		
1.a. Spontaneously Resolving Acute Rejection	1	0		
1.b. Corticosteroid Sensitive Acute Rejection	6	2		
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: Number of Participants with Biopsy-proven Acute Rejection Episodes (BPARs)

End point title	Number of Participants 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: participants				
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 participants 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: participants				
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 participants died 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 ^[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 participants 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 participant 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 participants in the tacrolimus group had efficacy failure due to an unknown outcome as these 3 participants discontinued early from the study. 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: participants				
number (not applicable)				
Graft loss	0	0		
BPAR	4	1		
Death	0	0		
Unknown	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)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.1
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Reporting groups

Reporting group title	Tacrolimus (Part A + B)
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Reporting group description:

Participants 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 A + B)
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Reporting group description:

Participants 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 A + B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 24 (62.50%)	13 / 20 (65.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 24 (8.33%)	5 / 20 (25.00%)	
occurrences causally related to treatment / all	1 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			

subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood phosphorus decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain scan abnormal			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histology abnormal			
subjects affected / exposed	2 / 24 (8.33%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Device connection issue			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site pain			

subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible posterior leukoencephalopathy syndrome			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary fistula			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Focal segmental glomerulosclerosis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 24 (8.33%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Residual urine			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis bacterial			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

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

subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	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 A + B)	
Total subjects affected by non-serious adverse events subjects affected / exposed	22 / 24 (91.67%)	19 / 20 (95.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Papilloma subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	9 / 24 (37.50%) 9	6 / 20 (30.00%) 6	
Surgical and medical procedures Post procedural drainage subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 4	1 / 20 (5.00%) 1	
General disorders and administration site conditions Bloody discharge subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0 3 / 24 (12.50%) 3 1 / 24 (4.17%) 1 3 / 24 (12.50%) 4	1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 2 / 20 (10.00%) 2 3 / 20 (15.00%) 4	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Social circumstances Exposure to communicable disease subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 20 (0.00%) 0	

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

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Investigations			
Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	3 / 20 (15.00%) 4	
Blood iron decreased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Blood magnesium decreased subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 20 (0.00%) 0	
Blood phosphorus decreased subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	1 / 20 (5.00%) 1	
Blood urea increased subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	1 / 20 (5.00%) 2	
Body temperature increased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Heart rate decreased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Immunosuppressant drug level decreased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Immunosuppressant drug level increased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	2 / 20 (10.00%) 2	
Oxygen saturation decreased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Urine output decreased			

subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 20 (0.00%) 0	
Weight increased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Injury, poisoning and procedural complications			
Complications of transplanted kidney subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 20 (5.00%) 1	
Drug dispensing error subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 2	
Expired drug administered subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Wrist fracture subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Cardiac disorders			
Arrhythmia supraventricular subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Pericardial effusion subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 20 (0.00%) 0	
Tachycardia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	4 / 20 (20.00%) 4	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Reversible posterior leukoencephalopathy syndrome			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Tremor subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 20 (5.00%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 6	4 / 20 (20.00%) 5	
Leukopenia subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	1 / 20 (5.00%) 1	
Neutropenia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 20 (5.00%) 2	
Thrombocytopenia subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	1 / 20 (5.00%) 1	
Eye disorders			
Conjunctivitis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 20 (0.00%) 0	
Visual impairment subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 20 (5.00%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	2 / 20 (10.00%) 4	
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 20 (10.00%) 2	
Aphthous stomatitis			

subjects affected / exposed	3 / 24 (12.50%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Constipation			
subjects affected / exposed	2 / 24 (8.33%)	3 / 20 (15.00%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	11 / 24 (45.83%)	11 / 20 (55.00%)	
occurrences (all)	12	19	
Dyspepsia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Gastrointestinal pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 24 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Lip oedema			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	3 / 24 (12.50%)	4 / 20 (20.00%)	
occurrences (all)	4	4	
Peritoneal effusion			
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	5 / 24 (20.83%)	5 / 20 (25.00%)	
occurrences (all)	8	7	
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Cholestasis subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Jaundice subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 20 (5.00%) 1	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 20 (10.00%) 2	
Night sweats subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Skin lesion subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Renal and urinary disorders			
Detrusor sphincter dyssynergia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Nocturia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Renal failure subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Back pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	3 / 20 (15.00%) 3	
Muscle spasms subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 20 (10.00%) 2	

Osteopenia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Infections and infestations			
Acute tonsillitis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 20 (5.00%) 1	
Bronchitis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 20 (5.00%) 1	
Bronchopneumonia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 20 (0.00%) 0	
Cytomegalovirus infection subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	2 / 20 (10.00%) 2	
Cytomegalovirus viraemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 2	1 / 20 (5.00%) 1	
Epstein-Barr viraemia subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	0 / 20 (0.00%) 0	
Epstein-Barr virus infection subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	2 / 20 (10.00%) 2	
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	1 / 20 (5.00%) 2	
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Herpes zoster subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 20 (5.00%) 1	
Lower respiratory tract infection			

subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Nasopharyngitis		
subjects affected / exposed	2 / 24 (8.33%)	2 / 20 (10.00%)
occurrences (all)	2	2
Oral candidiasis		
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)
occurrences (all)	1	1
Oral herpes		
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Pharyngitis		
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)
occurrences (all)	1	1
Pyelonephritis		
subjects affected / exposed	0 / 24 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	2
Respiratory tract infection viral		
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Rhinitis		
subjects affected / exposed	2 / 24 (8.33%)	2 / 20 (10.00%)
occurrences (all)	3	3
Rubella		
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Tonsillitis		
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)
occurrences (all)	1	1
Upper respiratory tract infection		
subjects affected / exposed	4 / 24 (16.67%)	4 / 20 (20.00%)
occurrences (all)	4	6
Urinary tract infection		

subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 24 (12.50%)	1 / 20 (5.00%)	
occurrences (all)	4	2	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Glucose tolerance impaired			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypercalcaemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Hyperuricaemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Hyponatraemia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)	
occurrences (all)	1	1	

Hypophosphataemia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Metabolic acidosis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Vitamin D deficiency			
subjects affected / exposed	2 / 24 (8.33%)	1 / 20 (5.00%)	
occurrences (all)	2	1	

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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported