Clinical trial results:
A Phase II, Open-label, Multi-center Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Recipients Converted from a Prograf® Based Immunosuppressive Regimen to a Tacrolimus Prolonged Release, Advagraf® Based Immunosuppressive Regimen, Including a Long-term Follow-up

Summary

EudraCT number	2010-020925-42
Trial protocol	AT FR DE BE PL CZ IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	19 May 2017
First version publication date	19 May 2017

Trial information

Trial identification

Sponsor protocol code	PMR-EC-1206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01294020
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe, Ltd
Sponsor organisation address	2000 Hillswood Drive, Chertsey Surrey, 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?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	28 October 2016
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:

To compare the steady state area under the plasma concentration-time curve from time 0 to time 24 hours (AUC0-24h) of tacrolimus for tacrolimus prolonged release (Advagraf) with that of tacrolimus (Prograf) in stable pediatric allograft recipients after 1:1 (mg:mg) conversion from Prograf to Advagraf.

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 fed ral, 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). After enrollment, participants entered a 30-day screening period in Part A of the study during which time they were maintained on their routine twice daily tacrolimus (commercial Prograf) based immunosuppressive regimen, as determined by the Investigator and as supplied by the local hospital pharmacy.

Evidence for comparator: -

Actual start date of recruitment	25 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	United Kingdom: 15
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	35
Adolescents (12-17 years)	46
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Children aged 5 years to 16 years of age were enrolled in sites in 7 countries: Belgium, Czech Republic, Germany, 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:

Stable pediatric allograft recipients (children who previously received a single organ liver, kidney, heart, lung or intestinal transplantation [≥ 6 months post-transplant]) being treated with a tacrolimus based immunosuppressive regimen (≤ 3 months) who consented to enter this study and fulfilled all the eligibility criteria were enrolled.

Period 1

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

Arms

Arm title	Tacrolimus Prolonged Release (Part A)

Arm description:

Participants converted from their routine tacrolimus based immunosuppressive regimen to tacrolimus as a study medication twice daily on day 1 and continued to receive treatment up to day 7. On day 8, participants switched to tacrolimus prolonged release once daily and received treatment up to day 14 in Part A of the study.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus prolonged release
Investigational medicinal product code	FK506E
Other name	Advagraf, Astagraf XL, Graceptor, Prograf XL
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received tacrolimus prolonged release (strengths of 0.5 mg, 1 mg, 3 mg, 5 mg) with the same daily dose (1:1, mg:mg) after being coverted from tacrolimus on day 8, with the dose maintained up to day 14 in Part A of the study. Tacrolimus prolonged release capsules were taken orally once daily only in the morning, on an empty stomach, or at least 1 hour before or 2 to 3 hours after a meal.

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	FK506
Other name	Prograf
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received tacrolimus (strengths of 0.5 mg, 1 mg, 5 mg) with the same daily dose (1:1, mg:mg) as received during the 30-day screening period in Part A of the study. Tacrolimus capsules were taken orally twice daily, morning and evening, on an empty stomach or at least 1 hour before, or 2 to 3 hours after any meal.

Number of subjects in period 1	Tacrolimus Prolonged Release (Part A)
Started	81
Treated with study drug	81
Completed	78
Not completed	3
Adverse Event	1
Withdrawal of consent	1
Site staff could not cover the overnight visit	1

Period 2

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

Arms

Arm title	Tacrolimus Prolonged Release (Part B)

Arm description:

After Part A, participants continued to receive tacrolimus prolonged release once daily from day 15 up to the end of Part B of the study.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus prolonged release
Investigational medicinal product code	FK506E
Other name	Advagraf, Astagraf XL, Graceptor, Prograf XL
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants continued to receive tacrolimus prolonged release (strengths of 0.5 mg, 1 mg, 3 mg, 5 mg) with the same daily dose (1:1, mg:mg) from day 15 up to the end of Part B of the study but could be adjusted on the basis of trough drug measurement results. Tacrolimus prolonged release capsules were taken orally once daily only in the morning, on an empty stomach, or at least 1 hour before or 2 to 3 hours after a meal.

Number of subjects in period 2	Tacrolimus Prolonged Release (Part B)
Started	78
Completed	76
Not completed	2
Adverse Event	2

Baseline characteristics

Reporting groups	
Reporting group title	Tacrolimus Prolonged Release (Part A)

Reporting group description:

Participants converted from their routine tacrolimus based immunosuppressive regimen to tacrolimus as a study medication twice daily on day 1 and continued to receive treatment up to day 7. On day 8, participants switched to tacrolimus prolonged release once daily and received treatment up to day 14 in Part A of the study.

Reporting group values	Tacrolimus Prolonged Release (Part A)	Total	
Number of subjects	81	81	
Age categorical Units: Subjects			
5-7 years	11	11	
8-10 years	17	17	
11-13 years	31	31	
14-16 years	22	22	
Age continuous Units: years			
arithmetic mean	11.5		
standard deviation	± 2.87	-	
Gender categorical Units:			
Male	47	47	
Female	34	34	
Type of Organ Transplant Units: Subjects			
Kidney	48	48	
Liver	31	31	
Heart	2	2	
Other (Lung, Intestine)	0	0	

End points

End points reporting groups

Reporting group title	Tacrolimus Prolonged Release (Part A)
Reporting group description:	
Participants converted from their routine tacrolimus based immunosuppressive regimen to tacrolimus as a study medication twice daily on day 1 and continued to receive treatment up to day 7. On day 8, participants switched to tacrolimus prolonged release once daily and received treatment up to day 14 in Part A 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 from day 15 up to the end of Part B of the study.	
Subject analysis set title	Tacrolimus (Part A)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the pharmacokinetic analysis set who received tacrolimus twice daily on day 1 up to day 7 in Part A of the study.	
Subject analysis set title	Tacrolimus Prolonged Release (Part A)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the pharmacokinetic analysis set who received tacrolimus prolonged release once daily from day 8 up to day 14 in Part A of the study.	
Subject analysis set title	Tacrolimus Prolonged Release (Part A + B)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received tacrolimus prolonged release once daily from day 8 up to day 14 in Part A, and once daily from day 15 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 and Tacrolimus Prolonged Release

End point title	Area Under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours (AUC0-24h) for Tacrolimus and Tacrolimus Prolonged Release
End point description:	
The analysis population was the Pharmacokinetics Analysis Set (PKAS), which consisted of all participants who received at least 1 dose of study drug and who provided 2 complete pharmacokinetic profiles.	
End point type	Primary
End point timeframe:	
Day 7 (for tacrolimus) and day 14 (for tacrolimus prolonged release) at predose and 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	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	74		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	159.133 (± 32.7)	153.8194 (± 29.3)		

Statistical analyses

Statistical analysis title	AUC24 (steady-state systemic exposure) Comparison

Statistical analysis description:

The comparison of pharmacokinetic (PK) parameter AUC24 between tacrolimus and tacrolimus prolonged release was assessed with a mixed effects model on log-transformed PK parameters with treatment, organ transplant and age (continuous variable) at baseline as fixed effects and patient as random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=74.

Comparison groups	Tacrolimus Prolonged Release (Part A) v Tacrolimus (Part A)
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Geometric least squares (LS) mean ratio
Point estimate	96.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.31
upper limit	101.22

Notes:

[1] - The difference of LS means of log-transformed PK parameters between tacrolimus and tacrolimus prolonged release and its 90% CI are back-transformed to the raw scale and are expressed as percentages.

Secondary: Maximum Concentration (Cmax) of Tacrolimus and Tacrolimus Prolonged Release

End point title	Maximum Concentration (Cmax) of Tacrolimus and Tacrolimus Prolonged Release

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 prespecified in the protocol and is denoted as "99999."

End point type	Secondary

End point timeframe:

Day 7 (for tacrolimus) and day 14 (for tacrolimus prolonged release) at predose and 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	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	74		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				

Morning	11.792 (± 44.1)	11.048 (± 38.9)		
Evening	8.198 (± 40)	99999 (± 99999)		

Statistical analyses

Statistical analysis title	Cmax Comparison

Statistical analysis description:

The comparison of pharmacokinetic parameter Cmax between tacrolimus and tacrolimus prolonged release was assessed with a mixed effects model on log-transformed PK parameters with treatment, organ transplant and age (continuous variable) at baseline as fixed effects and patient as random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=74.

Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Geometric LS mean ratio
Point estimate	93.69
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.07
upper limit	100.81

Notes:

[2] - 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 are expressed as percentages. Morning Cmax in tacrolimus group was used for comparison with Cmax for participants in tacrolimus prolonged release group.

Secondary: Trough Concentration (C12) for Tacrolimus

End point title	Trough Concentration (C12) for Tacrolimus

End point description:

The analysis population was the PKAS.

End point type	Secondary

End point timeframe:

Day 7, 12 hours after dosing

End point values	Tacrolimus (Part A)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	4.753 (± 36.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (C24) for Tacrolimus and Tacrolimus Prolonged Release

End point title	Trough Concentration (C24) for Tacrolimus and Tacrolimus Prolonged Release
End point description:	
The analysis population was the PKAS.	
End point type	Secondary
End point timeframe:	
Days 7 and 14, 24 hours after dosing	

End point values	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	74		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	4.955 (± 37.6)	4.479 (± 31.7)		

Statistical analyses

Statistical analysis title	C24 Comparison
Statistical analysis description:	
The comparison of pharmacokinetic parameter C24 between tacrolimus and tacrolimus prolonged release was assessed with a mixed effects model on log-transformed PK parameters with treatment, organ transplant and age (continuous variable) at baseline as fixed effects and patient as random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=74.	
Comparison groups	Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A)
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Geometric LS mean ratio
Point estimate	90.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	85
upper limit	96.13

Notes:

[3] - 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 are expressed as percentages.

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

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

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 prespecified in the protocol and is denoted as "99999."

End point type	Secondary

End point timeframe:

Day 7 (for tacrolimus) and day 14 (for tacrolimus prolonged release) at predose and 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	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	74		
Units: hours				
median (full range (min-max))				
Morning	1.0584 (0.9 to 6)	1.9833 (0.917 to 24)		
Evening	3.9667 (0 to 12)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation between AUC24 and C24

End point title	Correlation between AUC24 and 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:

Day 7 (for tacrolimus) and day 14 (for tacrolimus prolonged release) at predose and 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	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	74		
Units: Pearson correlation coefficient				
number (not applicable)	0.84	0.89		

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. mFAS.

End point type	Secondary

End point timeframe:

Up to Week 54

End point values	Tacrolimus Prolonged Release (Part A + B)			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: participants				
1. Any Acute Rejections	2			
1.a. Spontaneously Resolving Acute Rejection	0			
1.b. Corticosteroid Sensitive Acute Rejection	1			
1.c. Corticosteroid Resistant Acute Rejection	1			
1.c.1 Resolved with further treatment	1			
1.c.2 Unresolved with further treatment	0			
1.c.3 Unresolved with no further treatment	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Biopsy Proven Acute Rejections (BPARs)

End point title	Number of Participants with Biopsy Proven Acute Rejections (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. mFAS.

End point type	Secondary

End point timeframe:

Up to Week 54

End point values	Tacrolimus Prolonged Release (Part A + B)			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: participants				
1. Biopsy proven acute rejections	1			
1.a. Spontaneously Resolving Acute Rejection	0			
1.b. Corticosteroid Sensitive Acute Rejection	0			
1.c. Corticosteroid Resistant Acute Rejection	1			
1.c.1 Resolved with further treatment	1			
1.c.2 Unresolved with further treatment	0			
1.c.3 Unresolved with no further treatment	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 (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 (mild, moderate, severe or indeterminate/borderline); for heart, according to Standardized Nomenclature of the International Society of Heart and Lung Transplantation (mild, moderate, severe). The analysis population was the modified Full Analysis Set (mFAS), which consisted of all participants who received at least 1 dose of tacrolimus prolonged release study drug.

End point type	Secondary

End point timeframe:

Up to Week 54

End point values	Tacrolimus Prolonged Release (Part A + B)			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: participants				
Kidney: Antibody-mediated rejection I	0			
Kidney: Antibody-mediated rejection II	1			
Kidney:Antibody-mediated rejection III	0			
Kidney:T cell mediated rejection IA	0			
Kidney:T cell mediated rejection IB	1			
Kidney:T cell mediated rejection IIA	0			
Kidney:T cell mediated rejection IIB	0			
Kidney:T cell mediated rejection III	0			
Liver: Mild	0			
Liver: Moderate	0			
Liver: Severe	0			
Liver: Indeterminate or borderline	0			
Heart: Mild	0			
Heart: Moderate	0			
Heart: Severe	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 tacrolimus as 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 54

End point values	Tacrolimus Prolonged Release (Part A + B)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[4]			
Units: days				
number (confidence interval 95%)	(to)			

Notes:

[4] - 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 tacrolimus as 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 54

End point values	Tacrolimus Prolonged Release (Part A + B)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[5]			
Units: days				
number (confidence interval 95%)	(to)			

Notes:

[5] - 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. The analysis population was the mFAS.

End point type	Secondary

End point timeframe:

Up to Week 54

End point values	Tacrolimus Prolonged Release (Part A + B)			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: participants	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (Part A)

End point title	Number of Participants with Adverse Events (Part A)

End point description:

Safety as 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 1 dose of any of the study drug (tacrolimus/tacrolimus prolonged release).

End point type	Secondary

End point timeframe:

From first dose of tacrolimus up to 7 days after last dose of tacrolimus prolonged release in Part A (up to 21 days)

End point values	Tacrolimus (Part A)	Tacrolimus Prolonged Release (Part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	79		
Units: participants				
AEs	8	14		
Drug-related AEs	1	2		
Deaths	0	0		
SAEs	0	0		
Drug-related SAEs	0	0		
Deaths Resulting from AEs	0	0		
AEs Leading to Permanent Discontinuation	0	0		
Drug-related AEs Leading to Permanent Discont.	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (Part B)

End point title	Number of Participants with Adverse Events (Part B)

End point description:

Safety as 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 mFAS.

End point type	Secondary

End point timeframe:

From first dose of tacrolimus prolonged release in Part A up to 7 days after last dose of tacrolimus prolonged release in Part B (up to 55 weeks)

End point values	Tacrolimus Prolonged Release (Part A + B)			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: participants				
AEs	67			
Drug-related AEs	28			
Deaths	0			
SAEs	19			
Drug-related SAEs	10			
Deaths Resulting from AEs	0			
AEs Leading to Permanent Discontinuation	1			
Drug-related AEs Leading to Permanent Discont.	1			

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 (tacrolimus/tacrolimus prolonged release) in Part A up to last dose of study drug (tacrolimus prolonged release) in Part B of the study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Tacrolimus

Reporting group description:

Participants converted from their routine tacrolimus based immunosuppressive regimen to tacrolimus as a study medication twice daily on day 1 and continued to receive treatment up to day 7 in Part A of the study.

Reporting group title	Tacrolimus prolonged release

Reporting group description:

Participants switched to tacrolimus prolonged release once daily on day 8 and received treatment up to day 14 in Part A and continued to receive tacrolimus prolonged release once daily from day 15 up to the end of Part B of the study.

Serious adverse events	Tacrolimus	Tacrolimus prolonged release	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 81 (0.00%)	19 / 79 (24.05%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunosuppressant drug level increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Expired drug administered			

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Benign intracranial hypertension			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug interaction			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar haemorrhage			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 81 (0.00%)	3 / 79 (3.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection bacterial			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tacrolimus	Tacrolimus prolonged release	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 81 (9.88%)	66 / 79 (83.54%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Skin papilloma			
subjects affected / exposed	0 / 81 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	4	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Vena cava thrombosis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Dermabrasion			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Enanthema			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Influenza like illness			

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Injection site pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 81 (0.00%)	6 / 79 (7.59%)	
occurrences (all)	0	8	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Cough			
subjects affected / exposed	0 / 81 (0.00%)	9 / 79 (11.39%)	
occurrences (all)	0	9	
Oropharyngeal pain			
subjects affected / exposed	0 / 81 (0.00%)	5 / 79 (6.33%)	
occurrences (all)	0	5	
Pharyngeal oedema			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Psychiatric disorders			

Abnormal behaviour			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Agitation			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Mood altered			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	2	
Blood creatinine increased			
subjects affected / exposed	0 / 81 (0.00%)	6 / 79 (7.59%)	
occurrences (all)	0	6	
Blood iron decreased			
subjects affected / exposed	0 / 81 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	3	
Blood pressure increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Blood triglycerides increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
C-reactive protein increased			

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Immunosuppressant drug level decreased			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
International normalised ratio increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Chronic allograft nephropathy			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	2	
Contusion			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Drug dispensing error			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Drug dose omission			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Expired drug administered			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Joint sprain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Nervous system disorders			
Clonus			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Epilepsy			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 81 (2.47%)	11 / 79 (13.92%)	
occurrences (all)	2	14	
Loss of consciousness			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Syncope vasovagal			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Leukocytosis			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Leukopenia			
subjects affected / exposed	0 / 81 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	3	
Lymphadenitis			

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	1 / 81 (1.23%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Eye disorders			
Chorioretinal atrophy			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Macular degeneration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Papilloedema			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 81 (1.23%)	5 / 79 (6.33%)	
occurrences (all)	1	7	
Aphthous stomatitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Constipation			

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Dental caries			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	0 / 81 (0.00%)	11 / 79 (13.92%)	
occurrences (all)	0	17	
Gastritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 81 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	3	
Odynophagia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 81 (1.23%)	8 / 79 (10.13%)	
occurrences (all)	1	10	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Liver disorder			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Cold sweat			

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Dermatitis				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Dermatitis allergic				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Dry skin				
subjects affected / exposed	1 / 81 (1.23%)	1 / 79 (1.27%)		
occurrences (all)	1	1		
Eczema				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Ephelides				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Erythema				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Hyperhidrosis				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Ingrowing nail				
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)		
occurrences (all)	0	2		
Intertrigo				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Nail disorder				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Photodermatosis				
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)		
occurrences (all)	0	1		
Pityriasis rosea				

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Scar pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	1 / 81 (1.23%)	1 / 79 (1.27%)	
occurrences (all)	1	1	
Subcutaneous nodule			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Pain in extremity			

subjects affected / exposed	1 / 81 (1.23%)	2 / 79 (2.53%)	
occurrences (all)	1	3	
Sever's disease			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Tendinous contracture			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Bronchitis			
subjects affected / exposed	0 / 81 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	4	
Cystitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Cytomegalovirus infection			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Gastroenteritis			
subjects affected / exposed	0 / 81 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	4	
Gastroenteritis viral			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	0 / 81 (0.00%)	6 / 79 (7.59%)	
occurrences (all)	0	11	
Oral fungal infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	1 / 81 (1.23%)	4 / 79 (5.06%)	
occurrences (all)	1	4	

Oropharyngeal candidiasis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Otitis externa			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	2 / 81 (2.47%)	8 / 79 (10.13%)	
occurrences (all)	2	12	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Purulent discharge			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	2	
Respiratory tract infection			
subjects affected / exposed	0 / 81 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	3	
Rhinitis			
subjects affected / exposed	1 / 81 (1.23%)	5 / 79 (6.33%)	
occurrences (all)	1	5	
Rotavirus infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Scarlet fever			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 81 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	5	
Tracheitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	

Tracheobronchitis mycoplasmal			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 81 (1.23%)	5 / 79 (6.33%)	
occurrences (all)	1	7	
Urinary tract infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	2	
Viral infection			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	3	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	3	
Hyperlipidaemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Iron deficiency			

subjects affected / exposed	0 / 81 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 81 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2013	This amendment added trough levels of tacrolimus as an inclusion factor, and updated details of study administration.
04 November 2013	This amendment added the Part C extension to the study (particularly for Italy and Poland).
23 April 2014	This amendment added the Part C extension to the study (particularly for Germany and Czech Republic).
01 December 2014	The protocol was reissued to combine all the individual country-specific amendments into 1 combined Country Protocol Amendment for Italy, Poland, German and Czech Republic.
28 June 2016	This amendment added UK sites to Part C of the study to comply with a UK-specific requirement.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported