Clinical trial results:
A Randomized, Open-Label, Comparative, Multi-Center Study to Assess the Safety and Efficacy of Prograf® (Tacrolimus)/MMF, and Extended Release (XL) Tacrolimus /MMF in de novo Kidney Transplant Recipients

Summary

EudraCT number	2015-002886-53
Trial protocol	Outside EU/EEA
Global end of trial date	26 April 2010

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	27 April 2016

Trial information

Trial identification

Sponsor protocol code	PRGXLKTx-0701-TW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00717678
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Taiwan, Inc
Sponsor organisation address	5 F., No. 10, Sec. 3, Min-Sheng E. Rd., Taipei, Taiwan,
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 April 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the safety and efficacy of tacrolimus/mycophenolate mofetil (MMF) and extended release (XL) tacrolimus/MMF in de novo kidney transplant recipients.

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:

All participants were administered: (1) Corticosteroids (initial dose of methylprednisolone 500-1000 mg [or equivalent dose], intravenous bolus, given at time of skin closure following the completion of transplant procedure [considered "Day 0"] and subsequent dosing of methylprednisolone 200 mg/day [or equivalent dose] on Day 1 post-transplant, followed by tapered oral prednisone use from 30 mg to 5 mg by 12 months post-transplant); (2) Antibody induction therapy (depending on patient's condition) consisting of interleukin-2 receptor antagonist monoclonal antibody, either daclizumab (Zenapax) or basilixmab (Simulect) per institutional protocol; and (3) Prophylaxis regimens for cytomegalovirus (CMV) and pneumocystis carinii pneumonia (PCP), standard antifungal prophylactic regimen and post-operative bacterial prophylactic regimen (per institutional protocol was given uniformly to all treatment groups).

Evidence for comparator: -

Actual start date of recruitment	26 December 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Taiwan: 73
Worldwide total number of subjects	73
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	68
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 5 sites in Taiwan.

Pre-assignment

Screening details:

Participants who were de novo kidney transplant recipients, consented to enter this study and fulfilled all the eligibility criteria were enrolled into the study. Screening assessments include recipient/donor serological status for cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B and C viruses, and human immunodeficiency virus (HIV).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tacrolimus XL/MMF

Arm description:

Participants who received tacrolimus extended release (XL) with mycophenolate mofetil (MMF) within 48 hours after the completion of a kidney transplant procedure.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus XL
Investigational medicinal product code	FK506E
Other name	Extended release tacrolimus, Advagraf
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received an initial dose of 0.15-0.20 mg/kg of tacrolimus XL orally within 48 hours of the completion of a kidney transplant procedure. Subsequent/maintenance doses were adjusted on the basis of clinical evidence of efficacy and occurrence of adverse events, and targeted whole blood trough level ranges (Days 0-90: 7-16 ng/mL; Days 90+: 5-15 ng/mL).

Investigational medicinal product name	MMF
Investigational medicinal product code	
Other name	CellCept
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received an initial dose of 0.5-1.0 g of MMF orally twice daily within 48 hours of the completion of a kidney transplant procedure. Subsequent doses can be changed (once daily, three times daily or total daily dose change) at the Investigator’s discretion, if clinically indicated (i.e., if tolerability was a concern).

Arm title	Tacrolimus/MMF

Arm description:

Participants who received tacrolimus with mycophenolate mofetil (MMF) within 48 hours after the completion of a kidney transplant procedure.

Arm type	Experimental

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 an initial dose of 0.075-0.10 mg/kg of tacrolimus orally twice daily within 48 hours of the completion of a kidney transplant procedure. Subsequent/maintenance doses were adjusted on the basis of clinical evidence of efficacy and occurrence of adverse events, and targeted whole blood trough level ranges (Days 0-90: 7-16 ng/mL; Days 90+: 5-15 ng/mL).

Investigational medicinal product name	MMF
Investigational medicinal product code	
Other name	CellCept
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received an initial dose of 0.5-1.0 g of MMF orally twice daily within 48 hours of the completion of a kidney transplant procedure. Subsequent doses can be changed (once daily, three times daily or total daily dose change) at the Investigator's discretion, if clinically indicated (i.e., if tolerability was a concern).

Number of subjects in period 1	Tacrolimus XL/MMF	Tacrolimus/MMF
Started	38	35
Safety population	38	31
Intent-to-treat population	38	31
Completed	31	25
Not completed	7	10
Discontinuation due to adverse events	1	3
Graft loss	3	2
Lost to follow-up	-	1
Non-compliant with protocol	-	4
Withdrew consent not related to AE	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Tacrolimus XL/MMF
Reporting group description:	
Participants who received tacrolimus extended release (XL) with mycophenolate mofetil (MMF) within 48 hours after the completion of a kidney transplant procedure.	
Reporting group title	Tacrolimus/MMF
Reporting group description:	
Participants who received tacrolimus with mycophenolate mofetil (MMF) within 48 hours after the completion of a kidney transplant procedure.	

Reporting group values	Tacrolimus XL/MMF	Tacrolimus/MMF	Total
Number of subjects	38	35	73
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	2	1	3
Adults (18-64 years)	34	34	68
From 65-84 years	2	0	2
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	42.9	43.9	
standard deviation	± 13.71	± 9.948	-
Gender categorical			
Units: Subjects			
Female	24	11	35
Male	14	20	34
Not reported due to protocol violation	0	4	4

End points

End points reporting groups

Reporting group title	Tacrolimus XL/MMF
Reporting group description:	
Participants who received tacrolimus extended release (XL) with mycophenolate mofetil (MMF) within 48 hours after the completion of a kidney transplant procedure.	
Reporting group title	Tacrolimus/MMF
Reporting group description:	
Participants who received tacrolimus with mycophenolate mofetil (MMF) within 48 hours after the completion of a kidney transplant procedure.	

Primary: Graft survival during the 6 months post-transplant

End point title	Graft survival during the 6 months post-transplant
End point description:	
Graft survival was defined as any participant who did not meet the definition of graft loss, which was defined as the death of the participant, retransplant or the permanent return to dialysis (greater than 30 days), or the participant became lost to follow-up. The analysis population was the intent-to-treat (ITT) population defined as randomized, transplanted participants who received at least one dose of their assigned study drug (tacrolimus/ tacrolimus XL) and had performed any study evaluation.	
End point type	Primary
End point timeframe:	
Day 0 up to 6 months post-transplant	

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants	35	29		

Statistical analyses

Statistical analysis title	Comparison of 6-month graft survival rates
Comparison groups	Tacrolimus XL/MMF v Tacrolimus/MMF
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.993 [1]
Method	Logrank

Notes:

[1] - The p-value was calculated by log-rank test to compare the survival distributions between treatment groups.

Primary: Patient survival during the 6 months post-transplant

End point title	Patient survival during the 6 months post-transplant[2]

End point description:

Patient survival was defined as any participant known to be alive at 6 months after transplant. The analysis population was the ITT population.

End point type	Primary

End point timeframe:

Day 0 up to 6 months post-transplant

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed since there were no deaths during the 6 months post-transplant.

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants	38	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with efficacy failure during 6 and 12 months post-transplant

End point title	Number of participants with efficacy failure during 6 and 12 months post-transplant

End point description:

Efficacy failure was defined as any participant who died, experienced a graft loss, had a biopsy proven acute rejection, or was lost to follow-up. The analysis population was the ITT population.

End point type	Secondary

End point timeframe:

Day 0 up to 6 and 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants				
6 months post-transplant	5	5		
12 months post-transplant	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with biopsy confirmed acute rejection (BCAR) (Banff grade ≥ I) during 6 and 12 months post-transplant

End point title	Number of participants with biopsy confirmed acute rejection (BCAR) (Banff grade ≥ I) during 6 and 12 months post-transplant

End point description:

Rejection episodes require biopsies for confirmation, and the pathologist at the site was responsible for grading all biopsies using the 1997 Banff criteria: Grade I/Mild-IA: Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross section or group of 10 tubular cells) and IB: Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells/tubular cross section or group of 10 tubular cells); Grade II/ Moderate-IIA: Cases with mild to moderate intimal arteritis in at least one arterial cross section and IIB: Cases with severe intimal arteritis comprising >25% of the luminal area lost in at least one arterial cross section; Grade III/Severe-Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic infiltrate in vessel. Analysis population was the ITT.

End point type	Secondary

End point timeframe:

Day 0 up to 6 and 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants				
6 months post-transplant	1	2		
12 months post-transplant	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first acute rejection episode

End point title	Time to first acute rejection episode

End point description:

Acute rejection was defined as first biopsy confirmed acute rejection from study drug first dose date. The analysis population was the ITT population. Due to the low number of participants who experienced BCAR, the Kaplan-Meier median time to first acute rejection could not be calculated and is denoted as "99999."

End point type	Secondary

End point timeframe:

Day 1 up to 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants requiring anti-lymphocyte antibody therapy for treatment of rejection

End point title	Number of participants requiring anti-lymphocyte antibody therapy for treatment of rejection

End point description:

If a participant had histologically proven Banff Grade II/Moderate (IIA: Cases with mild to moderate intimal arteritis in at least one arterial cross section and IIB: Cases with severe intimal arteritis comprising >25% of the luminal area lost in at least one arterial cross section) or III/Severe (Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic infiltrate in vessel rejection, then the patient could be initiated on antilymphocyte antibodies as per institutional protocol. The analysis population was the ITT population.

End point type	Secondary

End point timeframe:

Day 0 up to 6 and 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants				
6 months post-transplant	0	0		
12 months post-transplant	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of acute rejection

End point title	Severity of acute rejection

End point description:

The severity of acute rejections was assessed using the 1997 Banff criteria: Grade I/Mild-IA: Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross section or group of 10 tubular cells) and IB: Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells/tubular cross section or group of 10 tubular cells); Grade II/Moderate-IIA: Cases with mild to moderate intimal arteritis in at least one arterial cross section and IIB: Cases with severe intimal arteritis comprising >25% of the luminal area lost in at least one arterial cross section; Grade III/Severe - Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic infiltrate in vessel. "Not applicable" means no grade was given. Analysis population was participants in ITT with acute rejections.

End point type	Secondary

End point timeframe:

Day 0 up to 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2[3]		
Units: rejections				
Grade IA	1	0		
Not applicable	0	2		

Notes:

[3] - As the 2 acute rejections were on the borderline, they were graded as not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with multiple rejection episodes

End point title	Number of participants with multiple rejection episodes

End point description:

The analysis population was the ITT population.

End point type	Secondary

End point timeframe:

Day 0 up to 6 months and 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants				
6 months post-transplant	0	0		
12 months post-transplant	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinically treated acute rejection episodes

End point title	Number of participants with clinically treated acute rejection episodes

End point description:

Acute rejection episodes were treated with oral or intravenous (IV) corticosteroids with the dose not to exceed 1 gram/day for a maximum of 3-5 days. Subsequently, corticosteroids were tapered according to

institutional practice. The analysis population was the ITT population.

End point type	Secondary

End point timeframe:

Day 0 up to 6 months and 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants				
6 months post-transplant	1	2		
12 months post-transplant	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment failure

End point title	Number of participants with treatment failure

End point description:

Treatment failure is defined as discontinuation of randomized study drug for any reason. Participants who met the treatment failure definition were followed throughout the 12-month study.

End point type	Secondary

End point timeframe:

Day 0 up to 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants				
12 months post-transplant	7	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with renal function disorder

End point title	Percentage of participants with renal function disorder

End point description:

To detect acute rejection as early as possible, renal function was measured at each visit. Renal function disorder was defined as increased serum creatinine (>15%) as compared with baseline (Day 4). The

analysis population was the ITT population.

End point type	Secondary

End point timeframe:

Day 10, 14, 21, 28, 56, 84, 168, 274, 365 post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[4]	31[5]		
Units: percentage of participants				
number (not applicable)				
Day 10 [N=38,31]	5.3	3.2		
Day 14 [N=38,30]	10.5	13.3		
Day 21 [N=37,31]	8.1	3.2		
Day 28 [N=37,30]	13.5	6.7		
Day 56 [N=35,28]	22.9	10.7		
Day 84 [N=35,28]	28.6	10.7		
Day 168 [N=34,27]	20.6	3.7		
Day 274 [N=34,26]	26.5	11.5		
Day 365 [N=38,29]	18.4	17.2		

Notes:

[4] - See [N=X,Y]; N= number of participants for whom serum creatinine data was available.

[5] - See [N=X,Y]; N= number of participants for whom serum creatinine data was available.

Statistical analyses

No statistical analyses for this end point

Secondary: Patient survival during the 12 months post-transplant

End point title	Patient survival during the 12 months post-transplant

End point description:

Patient survival was defined as any participant known to be alive at the end of the study. The analysis population was the ITT population.

End point type	Secondary

End point timeframe:

Day 0 up to 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants	37	31		

Statistical analyses

Statistical analysis title	Comparison of 12-month patient survival rates
Comparison groups	Tacrolimus XL/MMF v Tacrolimus/MMF
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.38 [6]
Method	Logrank

Notes:

[6] - The p-value was calculated by log-rank test to compare the survival distributions between treatment groups.

Secondary: Graft survival during the 12 months post-transplant

End point title	Graft survival during the 12 months post-transplant

End point description:

Graft survival is defined as any participant who did not meet the definition of graft loss, which was defined as the death of the participant, retransplant or the permanent return to dialysis (greater than 30 days), or the participant became lost to follow-up. The analysis population was the ITT population.

End point type	Secondary

End point timeframe:

Day 0 up to 12 months post-transplant

End point values	Tacrolimus XL/MMF	Tacrolimus/MMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: participants	35	29		

Statistical analyses

Statistical analysis title	Comparison of 12-month graft survival rates
Comparison groups	Tacrolimus XL/MMF v Tacrolimus/MMF
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.993 [7]
Method	Logrank

Notes:

[7] - The p-value was calculated by log-rank test to compare the survival distributions between treatment groups.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to 28 days after last dose of study drug (up to 13 months)	
Adverse event reporting additional description:	
IIT/Safety population	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Tacrolimus XL/MMF
Reporting group description:	
Participants who received tacrolimus extended release (XL) with mycophenolate mofetil (MMF) within 48 hours after the completion of a kidney transplant procedure.	
Reporting group title	Tacrolimus/MMF
Reporting group description:	
Participants who received tacrolimus with mycophenolate mofetil (MMF) within 48 hours after the completion of a kidney transplant procedure.	

Serious adverse events	Tacrolimus XL/MMF	Tacrolimus/MMF	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 38 (50.00%)	15 / 31 (48.39%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 38 (5.26%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			

subjects affected / exposed	1 / 38 (2.63%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 38 (0.00%)	3 / 31 (9.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	0 / 38 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Cardiac murmur			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine analysis abnormal			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Albumin globulin ratio abnormal			
subjects affected / exposed	1 / 38 (2.63%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	2 / 38 (5.26%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
White blood cell disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			

subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
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 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pigmentation disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Albuminuria			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 38 (2.63%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			

subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 38 (7.89%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 38 (7.89%)	4 / 31 (12.90%)	
occurrences causally related to treatment / all	2 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 38 (2.63%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital candidiasis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	2 / 38 (5.26%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 38 (2.63%)	4 / 31 (12.90%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose tolerance impaired			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
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: 5 %

Non-serious adverse events	Tacrolimus XL/MMF	Tacrolimus/MMF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)	30 / 31 (96.77%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 38 (13.16%)	6 / 31 (19.35%)	
occurrences (all)	6	8	
Hypotension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 38 (5.26%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Haemorrhage			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 38 (5.26%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			

Face oedema			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 38 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	4 / 38 (10.53%)	6 / 31 (19.35%)	
occurrences (all)	5	9	
Influenza like illness			
subjects affected / exposed	1 / 38 (2.63%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Oedema			
subjects affected / exposed	1 / 38 (2.63%)	3 / 31 (9.68%)	
occurrences (all)	2	3	
oedema peripheral			
subjects affected / exposed	0 / 38 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	3	
Pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	2 / 38 (5.26%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	12 / 38 (31.58%)	12 / 31 (38.71%)	
occurrences (all)	15	23	
Dyspnoea			
subjects affected / exposed	3 / 38 (7.89%)	2 / 31 (6.45%)	
occurrences (all)	3	3	
Pleural effusion			
subjects affected / exposed	2 / 38 (5.26%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	4 / 38 (10.53%)	3 / 31 (9.68%)	
occurrences (all)	4	3	
Depression			
subjects affected / exposed	1 / 38 (2.63%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Insomnia			
subjects affected / exposed	8 / 38 (21.05%)	11 / 31 (35.48%)	
occurrences (all)	8	11	
Investigations			
Albumin globulin ratio abnormal			
subjects affected / exposed	4 / 38 (10.53%)	3 / 31 (9.68%)	
occurrences (all)	4	4	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 38 (10.53%)	4 / 31 (12.90%)	
occurrences (all)	5	4	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 38 (5.26%)	3 / 31 (9.68%)	
occurrences (all)	3	3	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	12 / 38 (31.58%)	12 / 31 (38.71%)	
occurrences (all)	16	16	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 38 (7.89%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 38 (15.79%)	4 / 31 (12.90%)	
occurrences (all)	6	4	
Headache			

subjects affected / exposed	3 / 38 (7.89%)	3 / 31 (9.68%)	
occurrences (all)	4	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 38 (18.42%)	9 / 31 (29.03%)	
occurrences (all)	8	10	
Leukocytosis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
White blood cell disorder			
subjects affected / exposed	6 / 38 (15.79%)	1 / 31 (3.23%)	
occurrences (all)	6	1	
Thrombocytopenia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 38 (15.79%)	10 / 31 (32.26%)	
occurrences (all)	6	14	
Constipation			
subjects affected / exposed	11 / 38 (28.95%)	10 / 31 (32.26%)	
occurrences (all)	13	12	
Diarrhoea			
subjects affected / exposed	11 / 38 (28.95%)	8 / 31 (25.81%)	
occurrences (all)	14	14	
Dyspepsia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Flatulence			
subjects affected / exposed	3 / 38 (7.89%)	2 / 31 (6.45%)	
occurrences (all)	3	3	
Gastritis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Gastrooesophageal reflux disease			

subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	3 / 38 (7.89%)	3 / 31 (9.68%)	
occurrences (all)	3	3	
Mouth ulceration			
subjects affected / exposed	4 / 38 (10.53%)	2 / 31 (6.45%)	
occurrences (all)	5	3	
Vomiting			
subjects affected / exposed	4 / 38 (10.53%)	4 / 31 (12.90%)	
occurrences (all)	4	5	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	3 / 38 (7.89%)	4 / 31 (12.90%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 38 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	3 / 38 (7.89%)	1 / 31 (3.23%)	
occurrences (all)	4	1	
Rash			
subjects affected / exposed	4 / 38 (10.53%)	3 / 31 (9.68%)	
occurrences (all)	4	5	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	4 / 38 (10.53%)	4 / 31 (12.90%)	
occurrences (all)	4	4	
Oliguria			
subjects affected / exposed	4 / 38 (10.53%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Urinary incontinence			

subjects affected / exposed	0 / 38 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	3 / 38 (7.89%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Back pain			
subjects affected / exposed	4 / 38 (10.53%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	1 / 38 (2.63%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Pharyngitis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Pneumonia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Rhinitis			
subjects affected / exposed	6 / 38 (15.79%)	5 / 31 (16.13%)	
occurrences (all)	6	5	
Upper respiratory tract infection			
subjects affected / exposed	5 / 38 (13.16%)	1 / 31 (3.23%)	
occurrences (all)	5	1	
Urinary tract infection			
subjects affected / exposed	9 / 38 (23.68%)	10 / 31 (32.26%)	
occurrences (all)	9	14	
Herpes simplex			
subjects affected / exposed	1 / 38 (2.63%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Herpes zoster			

subjects affected / exposed	0 / 38 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Sepsis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Cytomegalovirus infection			
subjects affected / exposed	4 / 38 (10.53%)	6 / 31 (19.35%)	
occurrences (all)	4	8	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	3 / 38 (7.89%)	5 / 31 (16.13%)	
occurrences (all)	3	5	
Diabetes mellitus			
subjects affected / exposed	2 / 38 (5.26%)	4 / 31 (12.90%)	
occurrences (all)	2	4	
Gout			
subjects affected / exposed	3 / 38 (7.89%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Hypercalcaemia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Hypercholesterolaemia			
subjects affected / exposed	3 / 38 (7.89%)	3 / 31 (9.68%)	
occurrences (all)	3	3	
Hyperglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 38 (21.05%)	8 / 31 (25.81%)	
occurrences (all)	8	9	
Hyperkalaemia			
subjects affected / exposed	6 / 38 (15.79%)	6 / 31 (19.35%)	
occurrences (all)	6	6	
Hyperlipidaemia			
subjects affected / exposed	9 / 38 (23.68%)	7 / 31 (22.58%)	
occurrences (all)	9	8	
Hypertriglyceridaemia			

subjects affected / exposed	0 / 38 (0.00%)	3 / 31 (9.68%)	
occurrences (all)	0	3	
Hyperuricaemia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Hypocalcaemia			
subjects affected / exposed	11 / 38 (28.95%)	10 / 31 (32.26%)	
occurrences (all)	12	11	
Hypokalaemia			
subjects affected / exposed	6 / 38 (15.79%)	3 / 31 (9.68%)	
occurrences (all)	6	3	
Hypomagnesaemia			
subjects affected / exposed	3 / 38 (7.89%)	0 / 31 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

At this time,the original analysis data sets have been destroyed by the outsourced group who conducted this study (per SOP) and only the raw data (not final) from the CRFs are available. Some data required for this disclosure were obtained from this.

Notes: