Clinical trial results:
Planned Transition to Sirolimus-based Therapy Versus Continued Tacrolimus-based Therapy in Renal Allograft Recipients.

Summary

EudraCT number	2008-006840-20
Trial protocol	ES IT DE
Global end of trial date	31 July 2013

Results information

Result version number	v2 (current)
This version publication date	03 August 2016
First version publication date	31 July 2015
Version creation reason	• Correction of full data set Errors identified within previously generated adverse event tables.

Trial information

Trial identification

Sponsor protocol code	0468E8-4500

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00895583
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 1800 7181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 1800 7181021, ClinicalTrials.gov_Inquiries@pfizer.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	Final
Date of interim/final analysis	14 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate whether planned transition between 90 and 150 days post-transplantation to Sirolimus (SRL) based therapy from Tacrolimus (TAC) based therapy was associated with a clinically relevant degree of improvement in renal function greater than or equal to [≥] 5 Milliliters Per Minute Per 1.73 Square Meters (mL/Min/m^2) compared to continuation of TAC-based therapy.

Protection of trial subjects:

The study was in compliance with with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Subjects remained on an inosine monophosphate dehydrogenase (IMPDH) inhibitor (mycophenolate mofetil [MMF] or mycophenolate sodium [MPS]; switching between the two was permitted). Subjects taking corticosteroids at the time of randomization had to be maintained on a minimum of 2.5 mg/day of prednisone (or the equivalent thereof); withdrawal which was not completed at least 30 days prior to randomization was prohibited.Subjects could be on study drug for up to maximum of 21 months.

Evidence for comparator: -

Actual start date of recruitment	05 June 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 140
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Brazil: 34
Worldwide total number of subjects	254
EEA total number of subjects	61

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)	0
Adults (18-64 years)	217
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study started on 05 June 2009 and ended on 31 July 2013. Subjects enrolled from Spain, Italy, United States, Argentina, Australia, Brazil.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sirolimus

Arm description:

Subjects received tacrolimus (extended release formulation not permitted) within 30 days of transplant, dosed according to center's standard of care. At 3-5 months post-transplant, subjects were randomized, tacrolimus was discontinued (withdrawal was to be completed within 2 weeks [maximum of 4 weeks] of sirolimus initiation).

Arm type	Experimental
Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	Rapamune
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received sirolimus tablets, orally, at a dose to achieve trough levels of 7-15 nanograms per milliliter (ng/mL) during the first year post-transplant, then 5-15 ng/mL. Subjects received study drug during the post-randomization period for up to a maximum of 21months post-transplant.

Arm title	Tacrolimus

Arm description:

Subjects received tacrolimus (extended-release formulation not permitted) within 30 days of transplant, dosed according to center's standard of care. At 3-5 months post-transplant, subjects were randomized and tacrolimus continued.

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects had to maintain the TAC-based immunosuppression therapy started prior to randomization, as per the center's standard of care. The use of TAC extended release formulations was not permitted.

Number of subjects in period 1	Sirolimus	Tacrolimus
Started	131	123
Completed	87	111
Not completed	44	12
Consent withdrawn by subject	4	2
Physician decision	3	1
Death	2	1
Not specified	-	1
Adverse event	28	4
Protocol Violation	1	-
Lost to follow-up	1	3
Lack of efficacy	5	-

Baseline characteristics

Reporting groups	
Reporting group title	Sirolimus
Reporting group description:	
Subjects received tacrolimus (extended release formulation not permitted) within 30 days of transplant, dosed according to center's standard of care. At 3-5 months post-transplant, subjects were randomized, tacrolimus was discontinued (withdrawal was to be completed within 2 weeks [maximum of 4 weeks] of sirolimus initiation).	
Reporting group title	Tacrolimus
Reporting group description:	
Subjects received tacrolimus (extended-release formulation not permitted) within 30 days of transplant, dosed according to center's standard of care. At 3-5 months post-transplant, subjects were randomized and tacrolimus continued.	

Reporting group values	Sirolimus	Tacrolimus	Total
Number of subjects	131	123	254
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	50.7	52.4	
standard deviation	± 13.03	± 12.05	-
Gender categorical			
Units: Subjects			
Female	42	46	88
Male	89	77	166

End points

End points reporting groups

Reporting group title	Sirolimus
Reporting group description:	
Subjects received tacrolimus (extended release formulation not permitted) within 30 days of transplant, dosed according to center's standard of care. At 3-5 months post-transplant, subjects were randomized, tacrolimus was discontinued (withdrawal was to be completed within 2 weeks [maximum of 4 weeks] of sirolimus initiation).	
Reporting group title	Tacrolimus
Reporting group description:	
Subjects received tacrolimus (extended-release formulation not permitted) within 30 days of transplant, dosed according to center's standard of care. At 3-5 months post-transplant, subjects were randomized and tacrolimus continued.	

Primary: Percentage of Subjects With Improvement of Greater Than or Equal to [≥]5 Milliliters Per Minute Per 1.73 Square Meters (mL/Min/m^2) in Calculated Glomerular Filtration Rate (GFR) at 24 Months Post-Transplantation (On-Therapy Analysis)

End point title	Percentage of Subjects With Improvement of Greater Than or Equal to [≥]5 Milliliters Per Minute Per 1.73 Square Meters (mL/Min/m^2) in Calculated Glomerular Filtration Rate (GFR) at 24 Months Post-Transplantation (On-Therapy Analysis)
End point description:	
GFR was calculated using the Modified Diet in Renal Disease (MDRD) equation using either serum creatinine traceable to isotope dilution mass spectrometry (IDMS) or serum creatinine not traceable to IDMS. On-Therapy Population (24 Months): all randomised subjects who remained on assigned study therapy through 24 months post-transplantation.	
End point type	Primary
End point timeframe:	
Baseline, Month 24	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	109		
Units: percentage of subjects				
number (not applicable)	33.7	42.2		

Statistical analyses

Statistical analysis title	GFR at 24 months
Comparison groups	Sirolimus v Tacrolimus

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239 [1]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.3

Notes:

[1] - Two-sided alpha equals (=) 0.05.

Secondary: Percentage of Subjects With Improvement of ≥5 mL/Min/m^2 in Calculated GFR at 12 Months Post-Transplantation (On-Therapy Analysis)

End point title	Percentage of Subjects With Improvement of ≥5 mL/Min/m^2 in Calculated GFR at 12 Months Post-Transplantation (On-Therapy Analysis)

End point description:

GFR was calculated using the MDRD equation using either serum creatinine traceable to IDMS (isotope dilution mass spectrometry) or serum creatinine not traceable to IDMS. On-Therapy Population (12 Months): all randomized subjects who remained on assigned study therapy through 12 months post-transplantation.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: percentage of subjects				
number (not applicable)	39.4	44.8		

Statistical analyses

Statistical analysis title	GFR at 12 months
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422 [2]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.4

Notes:

[2] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Improvement of ≥5 mL/Min/m^2 in Calculated GFR at 12 and 24 Months Post-Transplantation (Intent-to-Treat [ITT] Analysis)

End point title	Percentage of Subjects With Improvement of ≥5 mL/Min/m^2 in Calculated GFR at 12 and 24 Months Post-Transplantation (Intent-to-Treat [ITT] Analysis)

End point description:

GFR was calculated using the MDRD equation using either serum creatinine traceable to IDMS or serum creatinine not traceable to IDMS. ITT Population: all randomized subjects who received at least 1 dose of the assigned therapy after randomization. Missing GFR was imputed as follows: 1) GFR equals (=)0 after graft loss and 2) last observed value prior to missing was carried forward for death (with functioning graft), early termination or skipped assessment.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)				
Month 12	38.2	42.3		
Month 24	33.6	40.7		

Statistical analyses

Statistical analysis title	GFR at 12 month
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.524 [3]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.4

Notes:

[3] - Alpha was unadjusted.

Statistical analysis title	GFR at 24 Month
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.298 [4]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.2

Notes:

[4] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Improvement of ≥7.5 mL/Min/m^2 in Calculated GFR at 12 and 24 Months Post-Transplantation

End point title	Percentage of Subjects With Improvement of ≥7.5 mL/Min/m^2 in Calculated GFR at 12 and 24 Months Post-Transplantation

End point description:

GFR was calculated using the MDRD equation using either serum creatinine traceable to IDMS or serum creatinine not traceable to IDMS. ITT Population. Missing GFR was imputed as follows: 1) GFR=0 after graft loss and 2) last observed value prior to missing was carried forward for death (with functioning graft), early termination or skipped assessment.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)				
Month 12	24.4	35.8		
Month 24	25.2	30.9		

Statistical analyses

Statistical analysis title	GFR at 12 month
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055 [5]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1

Notes:

[5] - Alpha was unadjusted.

Statistical analysis title	GFR at 24 Month
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 [6]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.3

Notes:

[6] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Improvement of ≥10 mL/Min/m^2 in Calculated GFR at 12 and 24 Months Post-Transplantation

End point title	Percentage of Subjects With Improvement of ≥10 mL/Min/m^2 in Calculated GFR at 12 and 24 Months Post-Transplantation

End point description:

GFR was calculated using the MDRD equation using either serum creatinine traceable to IDMS or serum creatinine not traceable to IDMS. ITT Population. Missing GFR was imputed as follows: 1) GFR=0 after graft loss and 2) last observed value prior to missing was carried forward for death (with functioning graft), early termination or skipped assessment.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)				
Month 12	19.8	23.6		
Month 24	22.1	22		

Statistical analyses

Statistical analysis title	GFR at 12 month
Comparison groups	Tacrolimus v Sirolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.543 [7]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.5

Notes:

[7] - Alpha was unadjusted.

Statistical analysis title	GFR at 24 month
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [8]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.8

Notes:

[8] - Alpha was unadjusted.

Secondary: Calculated GFR Using MDRD (On-Therapy Analysis)

End point title	Calculated GFR Using MDRD (On-Therapy Analysis)

End point description:

GFR was calculated using the MDRD equation using either serum creatinine traceable to IDMS or serum

creatinine not traceable to IDMS. Baseline was defined as the last nonmissing assessment before or on the date of the first dose of test article. On-Therapy Population: all subjects who remained on assigned study therapy up to the point of discontinuation. n=number of subjects assessed for the specified parameter at a given visit.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12, 18, and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Baseline (n=131,123)	58.5 (± 14.3)	57.4 (± 14.1)		
Month 6 (n=125,120)	61.6 (± 14.9)	57.6 (± 14.2)		
Month 12 (n=109,116)	59.6 (± 16.4)	61.3 (± 14.3)		
Month 18 (n=99,111)	60 (± 15)	59.8 (± 17.1)		
Month 24 (n=86,109)	59.4 (± 18)	58.4 (± 14.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization in Calculated GFR Using MDRD (On-Therapy Analysis)

End point title	Change From Randomization in Calculated GFR Using MDRD (On-Therapy Analysis)

End point description:

GFR was calculated using the MDRD equation using either serum creatinine traceable to IDMS or serum creatinine not traceable to IDMS. Baseline was defined as the last nonmissing assessment before or on the date of the first dose of test article. On-Therapy Population; n=number of subjects assessed for the specified parameter at a given visit.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12, 18, and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: [units: mL/min/1.73 m^2]				
arithmetic mean (standard error)				
Month 6 (n=125,120)	2.7 (± 1.1)	0 (± 0.8)		
Month 12 (n=109,116)	1.5 (± 1.2)	3.4 (± 1.1)		
Month 18 (n=99,111)	2.2 (± 1.2)	1.5 (± 1.3)		
Month 24 (n=86,109)	1.2 (± 1.6)	0.6 (± 1.3)		

Statistical analyses

Statistical analysis title	Change from randomization at Month 6
Statistical analysis description:	
Change from randomization at Month 6. Analysis of covariance (ANCOVA) with treatment as a factor and baseline GFR as a covariate.	
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [9]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	5.5
Variability estimate	Standard error of the mean
Dispersion value	1.3

Notes:

[9] - Alpha was unadjusted.

Statistical analysis title	Change from randomization at Month 12
Statistical analysis description:	
Change from randomization at Month 12. ANCOVA with treatment as a factor and baseline GFR as a covariate.	
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215 [10]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	1.5

Notes:

[10] - Alpha was unadjusted.

Statistical analysis title	Change from randomization at Month 18

Statistical analysis description:

Change from randomization at Month 18. ANCOVA with treatment as a factor and baseline GFR as a covariate.

Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.722 [11]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	3.9
Variability estimate	Standard error of the mean
Dispersion value	1.7

Notes:

[11] - Alpha was unadjusted.

Statistical analysis title	Change from randomization at Month 24

Statistical analysis description:

Change from randomization at Month 24. ANCOVA with treatment as a factor and baseline GFR as a covariate.

Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71 [12]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	4.4
Variability estimate	Standard error of the mean
Dispersion value	1.9

Notes:

[12] - Alpha was unadjusted.

Secondary: Slope of Calculated GFR (MDRD) From Randomization to 24 Months Post-Transplantation (On-Therapy Analysis)

End point title	Slope of Calculated GFR (MDRD) From Randomization to 24 Months Post-Transplantation (On-Therapy Analysis)

End point description:

GFR was calculated using the MDRD equation using either serum creatinine traceable to IDMS or serum creatinine not traceable to IDMS. Timepoints were calculated as study days, relative to the time of randomization of study medication. All available on-therapy values were included. Observed data were multiplied by a scale factor of 365, expressing the slope as an annual change. On-Therapy analysis of the slope comprised the data collected from the on-therapy evaluations for all the subjects in the ITT population; data collected from subjects receiving sirolimus during the first 3 weeks post-randomization for safety monitoring were excluded from the analysis.

End point type	Secondary

End point timeframe:

Baseline, Month 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: mL/min/1.73 m^2 per year				
arithmetic mean (confidence interval 95%)	-0.9 (-2.7 to 0.8)	0.9 (-0.7 to 2.5)		

Statistical analyses

Statistical analysis title	Slope of calculated GFR

Statistical analysis description:

Slope difference (sirolimus [SRL] minus tacrolimus [TAC]). Random coefficient model with GFR as the dependent variable and study day as the independent variable.

Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.131
Method	Random coefficient model
Parameter estimate	Slope difference (SRL-TAC)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	0.5

Secondary: Serum Creatinine (On-Therapy Analysis)

End point title	Serum Creatinine (On-Therapy Analysis)

End point description:

Serum creatinine was measured in micromillimoles per liter (mcmol/L). Baseline was defined as the last nonmissing assessment before or on the date of the first dose of test article.
On-Therapy Population: all subjects who remained on assigned study therapy up to the point of discontinuation. n=number of subjects assessed for the specified parameter at a given visit.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12, 18, and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: mcmol/L				
arithmetic mean (standard deviation)				
Baseline (n=131,123)	118.3 (± 24.8)	117.7 (± 27.9)		
Month 6 (n=125,120)	113.9 (± 27.6)	117 (± 28.2)		
Month 12 (n=109,116)	119.6 (± 37.5)	109.4 (± 24.6)		
Month 18 (n=99,111)	116.9 (± 37.5)	114.2 (± 30.4)		
Month 24 (n=86,109)	122.9 (± 48.8)	117.5 (± 42.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization in Serum Creatinine (On-Therapy Analysis)

End point title	Change From Randomization in Serum Creatinine (On-Therapy Analysis)

End point description:

Serum creatinine was measured in mcmol/L. Baseline was defined as the last assessment prior to first administration of study drug. On-Therapy Population: all subjects who remained on assigned study therapy up to the point of discontinuation. n=number of subjects assessed for the specified parameter at a given visit.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12, 18, and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: mcmol/L				
arithmetic mean (standard error)				
Month 6 (n=125,120)	-4.1 (± 2)	0 (± 1.4)		
Month 12 (n=109,116)	-0.3 (± 2.9)	-7 (± 1.9)		
Month 18 (n=99,111)	-3 (± 2.5)	-1.9 (± 2.3)		
Month 24 (n=86,109)	3.2 (± 4.6)	0.5 (± 3.7)		

Statistical analyses

Statistical analysis title	Change from randomization at Month 6
Statistical analysis description:	
ANCOVA with treatment as a factor and baseline serum creatinine as a covariate.	
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105 [13]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	2.4

Notes:

[13] - Alpha was unadjusted.

Statistical analysis title	Change from randomization at Month 12
Statistical analysis description:	
ANCOVA with treatment as a factor and baseline serum creatinine as a covariate.	
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [14]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	14.3
Variability estimate	Standard error of the mean
Dispersion value	3.3

Notes:

[14] - Alpha was unadjusted.

Statistical analysis title	Change from randomization at Month 18
Statistical analysis description:	
ANCOVA with treatment as a factor and baseline serum creatinine as a covariate.	
Comparison groups	Sirolimus v Tacrolimus

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.955 [15]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	6.4
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[15] - Alpha was unadjusted.

Statistical analysis title	Change from randomization at Month 24

Statistical analysis description:

ANCOVA with treatment as a factor and baseline serum creatinine as a covariate.

Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.582 [17]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	14.6
Variability estimate	Standard error of the mean
Dispersion value	5.8

Notes:

[16] - Change from randomization at Month 24. ANCOVA with treatment as a factor and baseline serum creatinine as a covariate.
[17] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Biopsy-Confirmed Acute Rejection (BCAR), Graft Loss, or Death From Randomization to 24 Months Post-Transplantation

End point title	Percentage of Subjects With Biopsy-Confirmed Acute Rejection (BCAR), Graft Loss, or Death From Randomization to 24 Months Post-Transplantation

End point description:

Biopsy-confirmed acute rejection was defined according to updated Banff criteria (2007) for renal allograft rejection. Graft loss was defined as physical loss (nephrectomy or retransplantation), functional loss (requiring dialysis for greater than or equal to [≥]56 days with no return of graft function), or death. ITT Population.

End point type	Secondary

End point timeframe:

Post-randomization to Month 24 post-transplantation

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)	11.5	2.4		

Statistical analyses

Statistical analysis title	Randomization to 24 Months
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.006 [19]
Method	Fisher exact

Notes:

[18] - Alpha was unadjusted.

[19] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Graft Loss (Including Death) at 12 and 24 Months Post-Randomization

End point title	Percentage of Subjects With Graft Loss (Including Death) at 12 and 24 Months Post-Randomization

End point description:

Graft loss was defined as physical loss (nephrectomy or retransplantation), functional loss (requiring dialysis for ≥56 days with no return of graft function), or death. ITT Population

End point type	Secondary

End point timeframe:

Post-randomization to Months 12 and 24 Post-Transplantation

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)				
Month 12	0.8	0		
Month 24	3.8	0.8		

Statistical analyses

Statistical analysis title	Post-randomization to Month 12
Statistical analysis description:	
Post-randomization to Month 12 Post-transplantation.	
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [20]
Method	Fisher exact

Notes:

[20] - Alpha was unadjusted.

Statistical analysis title	Post-randomization to Month 24
Statistical analysis description:	
Post-randomization to Month 24 post-transplantation.	
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.215 [22]
Method	Fisher exact

Notes:

[21] - Post-randomization to Month 24 post-transplantation. Alpha was unadjusted.

[22] - Alpha was unadjusted.

Secondary: Percentage of Subjects With BCAR Post-Randomization to 6, 12, 18, and 24 Months Post-Transplantation

End point title	Percentage of Subjects With BCAR Post-Randomization to 6, 12, 18, and 24 Months Post-Transplantation
End point description:	
BCAR was defined according to updated Banff criteria (2007) for renal allograft rejection. ITT Population.	
End point type	Secondary
End point timeframe:	
Post-Randomization to 6, 12, 18, and 24 months Post-Transplantation	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: Subjects				
number (not applicable)				
Month 6	1.5	0		
Month 12	5.3	0.8		
Month 18	6.9	1.6		
Month 24	8.4	1.6		

Statistical analyses

Statistical analysis title	BCAR at Month 6
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.499 [23]
Method	Fisher exact

Notes:

[23] - Alpha was unadjusted.

Statistical analysis title	BCAR at Month 12
Comparison groups	Tacrolimus v Sirolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067 [24]
Method	Fisher exact

Notes:

[24] - Alpha was unadjusted.

Statistical analysis title	BCAR at Month 18
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061 [25]
Method	Fisher exact

Notes:

[25] - Alpha was unadjusted

Statistical analysis title	BCAR at Month 24
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [26]
Method	Fisher exact

Notes:

[26] - Alpha was unadjusted

Secondary: Percentage of Subjects With First On-Therapy BCAR From Transplantation Occurring at 12 and 24 Months

End point title	Percentage of Subjects With First On-Therapy BCAR From Transplantation Occurring at 12 and 24 Months

End point description:

Defined as the first BCAR occurring during the On-Therapy period based on the ITT population. Time to first BCAR was the days from transplantation to the date of BCAR. ITT Population.

End point type	Secondary

End point timeframe:
Months 12 and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)				
Month 12	5.1	0		
Month 24	9.3	0.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With BCAR by Severity of First BCAR and Time of Onset From Post-Randomization to 6, 12, 18, and 24 Months Post-Transplant

End point title	Number of Subjects With BCAR by Severity of First BCAR and Time of Onset From Post-Randomization to 6, 12, 18, and 24 Months Post-Transplant

End point description:

BCAR was categorized as antibody-mediated (AM) or T-cell. AM BCAR severity was graded as Grade I (mild), Grade II (moderate), and Grade III (severe). T-cell BCAR severity was graded as 'Grade Ia, Ib (mild), Grade IIa, IIb (moderate), and Grade III (severe). If a Subject had both T-cell BCAR and antibody-mediated BCAR on the first rejection, the subject was counted in each category. ITT Population.

End point type	Secondary

End point timeframe:
Months 6, 12, 18, and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: subjects				
number (not applicable)				
Month 6, AM Grade I	0	0		
Month 6, AM Grade II	0	0		
Month 6, AM Grade III	0	0		
Month 6, T-cell Grade Ia, Ib	2	0		
Month 6, T-cell Grade IIa, IIb	0	0		
Month 6, T-cell Grade III	0	0		
Month 12, AM Grade I	1	0		
Month 12, AM Grade II	0	0		
Month 12, AM Grade III	1	0		

Month 12, T-cell Grade Ia, Ib	5	0		
Month 12, T-cell Grade IIa, IIb	1	1		
Month 12, T-cell Grade III	0	0		
Month 18, AM Grade I	1	1		
Month 18, AM Grade II	0	0		
Month 18, AM Grade III	1	0		
Month 18, T-cell Grade Ia, Ib	7	1		
Month 18, T-cell Grade IIa, IIb	1	1		
Month 18, T-cell Grade III	0	0		
Month 24, AM Grade I	2	1		
Month 24, AM Grade II	1	0		
Month 24, AM Grade III	1	0		
Month 24, T-cell Grade Ia, Ib	8	1		
Month 24, T-cell Grade IIa, IIb	1	1		
Month 24, T-cell Grade III	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Antibody Use in Treatment of Acute Rejection

End point title	Percentage of Subjects With Antibody Use in Treatment of Acute Rejection

End point description:

Number of subjects who experienced an adverse event (AE) of rejection was used as the denominator in the determination of percentage of subjects with antibody use in treatment of acute rejection. Safety Population; only subjects with an AE of rejection were included in the analysis.

End point type	Secondary

End point timeframe:

On Therapy Period (up to 21 months post-randomization) and Off-Therapy Period (up to 24 months post-transplantation)

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: percentage of subjects				
number (not applicable)				
On-therapy Period	60	50		
Off-therapy Period	40	25		

Statistical analyses

Statistical analysis title	On-therapy Period
Comparison groups	Sirolimus v Tacrolimus

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [27]
Method	Fisher exact

Notes:

[27] - Alpha was unadjusted.

Statistical analysis title	Off-therapy Period
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [28]
Method	Fisher exact

Notes:

[28] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Anemia, Thrombocytopenia, or Leukopenia

End point title	Percentage of Subjects With Anemia, Thrombocytopenia, or Leukopenia

End point description:

Anemia was defined as hemoglobin less than or equal to (≤)10 grams per deciliter (g/dL); leukopenia was defined as white blood cell (WBC) count ≤2000 per cubic millimeters (/mm^3); and thrombocytopenia was defined as platelets ≤100,000/mm^3. Baseline was defined as the last nonmissing assessment before or on the date of the first dose of test article. Safety Population; n=number of subjects assessed for the specified parameter at a given visit.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	122		
Units: percentage of subjects				
number (not applicable)				
Baseline (n=131,122)	4.6	1.6		
Month 12 (n=110,116)	9.1	2.6		
Month 24 (n=89,112)	3.4	4.5		

Statistical analyses

Statistical analysis title	Baseline
Comparison groups	Sirolimus v Tacrolimus

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.284 [29]
Method	Fisher exact

Notes:

[29] - Alpha was unadjusted.

Statistical analysis title	Month 12
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [30]
Method	Fisher exact

Notes:

[30] - Alpha was unadjusted.

Statistical analysis title	Month 24
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [31]
Method	Fisher exact

Notes:

[31] - Alpha was unadjusted.

Secondary: Change From Baseline (Pre-Randomization) to 12 and 24 Months Post-Transplantation in Fasting Lipid Parameters (Millimoles Per Liter [mmol/L])

End point title	Change From Baseline (Pre-Randomization) to 12 and 24 Months Post-Transplantation in Fasting Lipid Parameters (Millimoles Per Liter [mmol/L])

End point description:

Parameters assessed included total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C); collected when subject was in a fasting state. Safety Population; n=number of subjects assessed for the specified parameter at a given visit.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	107		
Units: units: mmol/L				
arithmetic mean (standard error)				
TC, Change at Month 12 (n=96,107)	0.66 (± 0.1)	-0.12 (± 0.07)		
TC, Change at Month 24 (n=74,88)	0.51 (± 0.14)	-0.08 (± 0.09)		
HDL-C, Change at Month 12 (n=90,99)	0 (± 0.03)	0.01 (± 0.02)		
HDL-C, Change at Month 24 (n=69,81)	0.01 (± 0.04)	0.01 (± 0.03)		
LDL-C, Change at Month 12 (n=87,98)	0.43 (± 0.09)	-0.06 (± 0.07)		
LDL-C, Change at Month 24 (n=66,78)	0.34 (± 0.13)	-0.06 (± 0.08)		
Triglycerides, Change at Month 12 (n=94,104)	0.47 (± 0.11)	-0.18 (± 0.07)		
Triglycerides, Change at Month 24 (n=73,86)	0.43 (± 0.1)	0.07 (± 0.12)		

Attachments (see zip file)	Statistical analysis/Statistical analysis OM 18.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring Anti-Hypertensive Medication, Diabetes Agents, Lipid-Lowering Agents, or Erythropoiesis Stimulating Agents (ESAs)

End point title	Percentage of Subjects Requiring Anti-Hypertensive Medication, Diabetes Agents, Lipid-Lowering Agents, or Erythropoiesis Stimulating Agents (ESAs)
End point description: ITT Population.	
End point type	Secondary
End point timeframe: Baseline, Months 12 and 24	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)				
Baseline, Anti-hypertensives	95.4	92.7		
Month 12, Anti-hypertensives	75.6	69.9		
Month 24, Anti-hypertensives	61.8	65.9		
Baseline, Diabetes agents (insulin)	46.6	47.2		
Month 12, Diabetes agents (insulin)	26	26		
Month 24, Diabetes agents (insulin)	18.3	25.2		
Baseline, Diabetes agents (non-insulin)	14.5	17.9		
Month 12, Diabetes agents (non-insulin)	10.7	13.8		

Month 24, Diabetes agents (non-insulin)	9.2	13		
Baseline, Lipid-lowering agents	46.6	60.2		
Month 12, Lipid-lowering agents	55.7	54.5		
Month 24, Lipid-lowering agents	47.3	49.6		
Baseline, ESAs	50.4	43.1		
Month 12, ESAs	7.6	2.4		
Month 24, ESAs	3.8	2.4		

Statistical analyses

Statistical analysis title	Anti-hypertensives, Baseline
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.429 [32]
Method	Fisher exact

Notes:

[32] - Alpha was unadjusted.

Statistical analysis title	Anti-hypertensives, Month 12
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.326 [33]
Method	Fisher exact

Notes:

[33] - Alpha was unadjusted.

Statistical analysis title	Anti-hypertensives, Month 24
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.517 [34]
Method	Fisher exact

Notes:

[34] - Alpha was unadjusted.

Statistical analysis title	Diabetes agents (insulin), Baseline
Comparison groups	Sirolimus v Tacrolimus

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [35]
Method	Fisher exact

Notes:
[35] - Alpha was unadjusted.

Statistical analysis title	Diabetes agent (insulin), Month 12
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [36]
Method	Fisher exact

Notes:
[36] - Alpha was unadjusted.

Statistical analysis title	Diabetes agent (non-insulin), Baseline
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.498 [37]
Method	Fisher exact

Notes:
[37] - Alpha was unadjusted.

Statistical analysis title	Diabetes agent (non-insulin), Month 12
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.566 [38]
Method	Fisher exact

Notes:
[38] - Alpha was unadjusted.

Statistical analysis title	Diabetes agent (non-insulin), Month 24

Statistical analysis description:
Diabetes agent (non-insulin), Month 24.

Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.423 [39]
Method	Fisher exact

Notes:
[39] - Alpha was unadjusted.

Statistical analysis title	Lipid-lowering agents, Baseline
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033 [40]
Method	Fisher exact

Notes:
[40] - Alpha was unadjusted.

Statistical analysis title	Lipid-lowering agents, Month 12
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9 [41]
Method	Fisher exact

Notes:
[41] - Alpha was unadjusted.

Statistical analysis title	Lipid-lowering agents, Month 24
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.802 [42]
Method	Fisher exact

Notes:
[42] - Alpha was unadjusted.

Statistical analysis title	ESAs, Baseline
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26 [43]
Method	Fisher exact

Notes:
[43] - Alpha was unadjusted.

Statistical analysis title	ESAs, Month 12
Comparison groups	Sirolimus v Tacrolimus

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086 [44]
Method	Fisher exact

Notes:

[44] - Alpha was unadjusted.

Statistical analysis title	ESAs, Month 24
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723 [45]
Method	Fisher exact

Notes:

[45] - Alpha was unadjusted.

Secondary: Spot and 24 Hour Urine Protein to Creatinine Ratio (UPr/Cr)

End point title	Spot and 24 Hour Urine Protein to Creatinine Ratio (UPr/Cr)

End point description:

Baseline was defined as the last nonmissing assessment before or on the date of the first dose of test article. Safety Population; n=number of subjects assessed for the specified parameter at a given visit.

End point type	Secondary

End point timeframe:

Baseline and Months 12 and 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	120		
Units: UPr/Cr				
arithmetic mean (standard deviation)				
Baseline (n=127,120)	0.18 (± 0.1413)	0.195 (± 0.1477)		
Month 12 (n=112,108)	0.353 (± 0.3677)	0.208 (± 0.2234)		
Month 24 (n=102,106)	0.51 (± 0.7887)	0.3 (± 0.6154)		

Statistical analyses

Statistical analysis title	Change from pre-randomization at Month 12

Statistical analysis description:

Treatment ratio (SRC/TAC) in adjusted geometric mean fold-change from baseline. ANCOVA model with change in the logarithmic Upr/Cr as dependent variable, treatment and logarithmic pre-randomization value as covariate.

Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [46]
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.38
upper limit	2.11

Notes:

[46] - Alpha was unadjusted.

Statistical analysis title	Change from pre-randomization at Month 24

Statistical analysis description:

Treatment ratio (SRC/TAC) in adjusted geometric mean fold-change from baseline. ANCOVA model with change in the logarithmic Upr/Cr as dependent variable, treatment and logarithmic pre-randomization value as covariate.

Comparison groups	Tacrolimus v Sirolimus
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [47]
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.39
upper limit	2.26

Notes:

[47] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Block (ARB) Use

End point title	Percentage of Subjects With Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Block (ARB) Use

End point description:

Included ACEI or ARB use prior to randomization, during the on-therapy period (up to 19 to 21 months post randomization) and the off-therapy period (up to 24 months post-transplantation). ITT Population.

End point type	Secondary

End point timeframe:

Pre-randomization, On-Therapy Period (up to 21 months post-randomization), and Off-Therapy Period (up to 24 months post-transplantation)

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)				
Pre-randomization	46.6	46.3		
On-Therapy Period	43.5	29.3		
Off-Therapy Period	32.1	18.7		

Statistical analyses

Statistical analysis title	Pre-randomization
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [48]
Method	Fisher exact

Notes:

[48] - Alpha was unadjusted.

Statistical analysis title	On-Therapy Period
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [49]
Method	Fisher exact

Notes:

[49] - Alpha was unadjusted.

Statistical analysis title	Off-Therapy Period
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [50]
Method	Fisher exact

Notes:

[50] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Stomatitis

End point title	Percentage of Subjects With Stomatitis

End point description:

Includes adverse events based on categorization by the investigator as stomatitis, regardless of the event preferred term in Medical Dictionary for Regulatory Activities (MedDRA). Safety Population.

End point type	Secondary

End point timeframe:

From randomization up to 24 months after transplantation (On-Therapy)

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)	28.2	1.6		

Statistical analyses

Statistical analysis title	Subjects with Stomatitis
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [51]
Method	Fisher exact

Notes:

[51] - Alpha was unadjusted.

Secondary: Percentage of Subjects Requiring Treatment for Stomatitis by Treatment Type

End point title	Percentage of Subjects Requiring Treatment for Stomatitis by Treatment Type

End point description:

Included treatments (analgesics, dental paste, topical antifungal, topical steroids, or other) prior to randomization, during the on-therapy period (up to 19 to 21 months post-randomization) and the off-therapy period (up to 24 months post-transplantation). ITT Population

End point type	Secondary

End point timeframe:

On-Therapy Period (up to 21 months post-randomization) and Off-Therapy Period (up to 24 months post-transplantation).

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)				
On-Therapy Period, any treatment	17.6	2.4		
Off-Therapy Period, any treatment	3.1	1.6		
On-Therapy, analgesics	0.8	0		
On-Therapy, dental paste	3.8	0.8		
On-Therapy, topical steroids	5.3	0		

On-Therapy, other	10.7	2.4		
Off-Therapy, topical steroids	1.5	0		
Off-Therapy, other	1.5	1.6		

Statistical analyses

Statistical analysis title	On-Therapy Period
Statistical analysis description:	
On-Therapy Period, any treatment.	
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [52]
Method	Fisher exact

Notes:

[52] - Alpha was unadjusted.

Statistical analysis title	Off-Therapy Period
Statistical analysis description:	
Off-Therapy Period, any treatment.	
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.685 [53]
Method	Fisher exact

Notes:

[53] - Alpha was unadjusted.

Secondary: Change From Pre-Randomization to 12 Months Post-Transplantation in Hemoglobin A1C (Liter Per Liter [L/L])

End point title	Change From Pre-Randomization to 12 Months Post-Transplantation in Hemoglobin A1C (Liter Per Liter [L/L])
End point description:	
Ratio of hemoglobin A1c to normal hemoglobin. Safety Population.	
End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	98		
Units: L/L				
arithmetic mean (standard error)	0 (± 0)	0 (± 0)		

Attachments (see zip file)	Statistical analysis/Statstical analysis OM 24.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Randomization to 12 Months Post-Transplantation in Fasting Glucose (mmol/L)

End point title	Change From Pre-Randomization to 12 Months Post-Transplantation in Fasting Glucose (mmol/L)
End point description: Safety Population.	
End point type	Secondary
End point timeframe: Baseline, Month 12	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	112		
Units: mmol				
arithmetic mean (standard error)	-0.5 (± 0.31)	-0.23 (± 0.2)		

Attachments (see zip file)	Statistical attachment/Statistical analysis OM 25.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Randomization to 12 Months Post-Transplantation in Fasting Insulin (Picomoles Per Liter [Pmol/L])

End point title	Change From Pre-Randomization to 12 Months Post-Transplantation in Fasting Insulin (Picomoles Per Liter [Pmol/L])
End point description: Safety Population.	
End point type	Secondary
End point timeframe: Baseline, Month 12	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	84		
Units: pmol/L				
arithmetic mean (standard error)	27.25 (± 21.97)	17.14 (± 11.85)		

Attachments (see zip file)	Statistical analysis/Statistical analysis OM 26.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Randomization to 12 Months Post-Transplantation in Weight (Kilograms [kg])

End point title	Change From Pre-Randomization to 12 Months Post-Transplantation in Weight (Kilograms [kg])
End point description: Safety Population.	
End point type	Secondary
End point timeframe: Baseline, Month 12	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	113		
Units: kg				
arithmetic mean (standard error)	1.61 (± 0.51)	2.03 (± 0.44)		

Attachments (see zip file)	Statistical analysis/Statistical analysis OM 27.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Randomization to 12 Months Post-Transplantation in Waist Circumference(Centimeters [cm])

End point title	Change From Pre-Randomization to 12 Months Post-Transplantation in Waist Circumference(Centimeters [cm])

End point description: Safety Population.	
End point type	Secondary
End point timeframe: Baseline, Month 12	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	105		
Units: cm				
arithmetic mean (standard error)	1.13 (± 0.73)	2.21 (± 1)		

Attachments (see zip file)	Statistical analysis/Statistical analysis OM 28.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Randomization to 12 Months Post-Transplantation in Homeostasis Model Assessment Insulin Resistance (HOMA-IR; Fasting)

End point title	Change From Pre-Randomization to 12 Months Post-Transplantation in Homeostasis Model Assessment Insulin Resistance (HOMA-IR; Fasting)
End point description: The HOMA-IR measures insulin resistance based on fasting glucose and insulin measurements: HOMA-IR = fasting plasma glucose (mmol/L) multiplied by (*) fasting plasma insulin in microunits per liter (µU/L) divided by (/) 22.5. Subjects taking insulin within 12 hours were excluded from the analysis. Safety Population.	
End point type	Secondary
End point timeframe: Baseline, Month 12	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	77		
Units: insulin resistance score				
arithmetic mean (standard error)	1.14 (± 1.37)	1.1 (± 0.7)		

Attachments (see zip file)	Statistical analysis/Statistical analysis OM 29.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Randomization to 12 Months Post-Transplantation in HOMA-Beta Cell (HOMA-B; Fasting)

End point title	Change From Pre-Randomization to 12 Months Post-Transplantation in HOMA-Beta Cell (HOMA-B; Fasting)

End point description:

The Homeostasis Model Assessment (HOMA) estimates steady state beta cell function (%B) as a percentage of a normal reference population. HOMA-B = 20 * insulin (µU/L) / fasting plasma glucose (mmol/L) minus (-) 3.5 Subjects taking insulin within 12 hours were excluded from the analysis. Safety Population.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	77		
Units: percentage beta cell function				
arithmetic mean (standard error)	230.23 (± 214.68)	26.05 (± 21.99)		

Attachments (see zip file)	Statistical analysis/Statistical analysis OM 30.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Randomization to 12 Months Post-Transplantation in Body Mass Index (BMI; in Kilograms Per Square Meter [kg/m^2])

End point title	Change From Pre-Randomization to 12 Months Post-Transplantation in Body Mass Index (BMI; in Kilograms Per Square Meter [kg/m^2])

End point description:

BMI = Weight (kg)/(Height*Height) (square meters [m^2]). Safety Population.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	109		
Units: kg/m^2				
arithmetic mean (standard error)	0.53 (± 0.18)	0.75 (± 0.15)		

Attachments (see zip file)	Statistical analysis/statistical analysis OM 31.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With New-Onset Diabetes

End point title	Percentage of Subjects With New-Onset Diabetes

End point description:

Subjects were considered as having new onset diabetes during the On-therapy period if any of the below events emerged from baseline to Month 24: 1) at least 30 days continuous, or at least 25 days non-stop (without gap) use of any diabetic treatment after randomization; 2) a fasting glucose greater than or equal to (≥)126 milligrams per deciliter (mg/dL) after randomization; or 3) a non-fasting glucose ≥200 mg/dL after randomization, were included in the new-onset diabetes population. Events at Months 12 or 24 occurred from baseline to On-therapy Month 12 and from On-therapy Months 12 to 24, respectively. Safety Population. n=number of subjects assessed for the specified parameter at a given visit.

End point type	Secondary

End point timeframe:

From Baseline to On-Therapy Month 12, from Baseline to On-Therapy Month 24, and from On-Therapy Month 12 up to On-Therapy Month 24

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82[54]	72[55]		
Units: percentage of subjects				
number (not applicable)				
New onset (n=82,72)	18.3	5.6		
New onset at 1 year (n=82,72)	14.6	2.8		
New onset at 2 years (n=70,70)	4.3	2.9		

Notes:

[54] - Number of subjects analyzed

[55] - Number of subjects analyzed

Statistical analyses

Statistical analysis title	From Baseline up to On-Therapy Month 24

Statistical analysis description:

New onset (from baseline up to On-Therapy Month 24).

Comparison groups	Sirolimus v Tacrolimus

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025 [56]
Method	Fisher exact

Notes:

[56] - Alpha was unadjusted.

Statistical analysis title	From Baseline up to On-Therapy Month 12

Statistical analysis description:

New onset at 1 year (from baseline up to On-Therapy Month 12).

Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [57]
Method	Fisher exact

Notes:

[57] - Alpha was unadjusted.

Statistical analysis title	From On-Therapy Month 12 to On-Therapy Month 24

Statistical analysis description:

New onset at 2 years (from On-Therapy Month 12 to On-Therapy Month 24).

Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [58]
Method	Fisher exact

Notes:

[58] - Alpha was unadjusted.

Secondary: Percentage of Subjects With New-Onset Diabetes Receiving Treatment for Diabetes (Insulin and Non-Insulin)

End point title	Percentage of Subjects With New-Onset Diabetes Receiving Treatment for Diabetes (Insulin and Non-Insulin)

End point description:

Subjects were considered as having new onset diabetes during the On-therapy period if any of the below events emerged between baseline and Month 12 or Month 24: 1) at least 30 days continuous, or at least 25 days non-stop (without gap) use of any diabetic treatment after randomization; 2) a fasting glucose ≥126 mg/dL after randomization; or 3) a non-fasting glucose ≥200 mg/dL after randomization. Safety Population. Only subjects with new-onset diabetes mellitus at the beginning of the analysis interval were included; those with pre-existing diabetes were excluded from the analysis.

End point type	Secondary

End point timeframe:

12 Months and 24 Months

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: percentage of subjects				
number (not applicable)				
Insulin (12-Month)	13.3	0		
Insulin (24-Month)	6.7	25		
Non-insulin (12-Month)	13.3	0		
Non-Insulin (24-Month)	13.3	0		

Statistical analyses

Statistical analysis title	Insulin (12-Month)
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [59]
Method	Fisher exact

Notes:

[59] - Alpha was unadjusted.

Statistical analysis title	Non-insulin (12-Month)
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [60]
Method	Fisher exact

Notes:

[60] - Alpha was unadjusted.

Statistical analysis title	Non-insulin (24-Month)
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.386 [61]
Method	Fisher exact

Notes:

[61] - Alpha was unadjusted.

Statistical analysis title	Insulin (24-Month)
Comparison groups	Sirolimus v Tacrolimus

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [62]
Method	Fisher exact

Notes:

[62] - Alpha was unadjusted.

Secondary: Percentage of Subjects With Infection

End point title	Percentage of Subjects With Infection

End point description:

Includes adverse events based on categorization by the investigator as 'infection', regardless of the event preferred term in MedDRA. Safety Population.

End point type	Secondary

End point timeframe:

From randomization up to 24 months after transplantation (On-Therapy)

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)	61.8	52		

Statistical analyses

Statistical analysis title	Subjects with infection
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.129
Method	Fisher exact

Secondary: Percentage of Subjects With Cytomegalovirus (CMV) Infection

End point title	Percentage of Subjects With Cytomegalovirus (CMV) Infection

End point description:

Includes adverse event terms reported by the investigator to be attributed to the organism 'cytomegalovirus', regardless of the preferred term in MedDRA. Safety Population.

End point type	Secondary

End point timeframe:

From randomization up to 24 months after transplantation (On-Therapy)

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)	3.1	3.3		

Statistical analyses

Statistical analysis title	Subjects with CMV infection
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Percentage of Subjects With Polyomavirus Infection	
End point title	Percentage of Subjects With Polyomavirus Infection
End point description: Includes adverse event terms reported by the investigator to be attributed to the organism 'polyomavirus', regardless of the preferred term in MedDRA. Safety Population	
End point type	Secondary
End point timeframe: From randomization up to 24 months after transplantation (On-Therapy)	

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)	3.8	7.3		

Statistical analyses

Statistical analysis title	Subjects with Polyomavirus Infection
Comparison groups	Tacrolimus v Sirolimus

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276
Method	Fisher exact

Secondary: Percentage of Subjects With Malignancy

End point title	Percentage of Subjects With Malignancy

End point description:

Includes any adverse events based on categorization by the investigator as 'malignancy', regardless of the event preferred term in MedDRA. Safety Population.

End point type	Secondary

End point timeframe:

From randomization up to 24 months after transplantation (On-Therapy)

End point values	Sirolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	123		
Units: percentage of subjects				
number (not applicable)	3.1	7.3		

Statistical analyses

Statistical analysis title	Subjects With Malignancy
Comparison groups	Sirolimus v Tacrolimus
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.158
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization up to 24 months after transplantation (plus [+]4 weeks) for adverse events (AEs) and serious AEs (SAEs).

Adverse event reporting additional description:

The same event may appear as both an AE and an SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v16.0

Reporting groups

Reporting group title	Tacrolimus

Reporting group description:

Subjects received tacrolimus (extended-release formulation not permitted) within 30 days of transplant, dosed according to center's standard of care. At 3-5 months post-transplant, subjects were randomized and tacrolimus continued. Subjects remained on an IMPDH inhibitor (MMF or MPS; switching between the two was permitted). Corticosteroids were maintained at a minimum of 2.5 mg/day of prednisone (or equivalent); withdrawal was prohibited after randomization. Subjects received study drug during the post-randomization period for up to a maximum of 18 months post-transplant.

Reporting group title	Sirolimus

Reporting group description:

Subjects received tacrolimus (extended-release formulation not permitted) within 30 days of transplant, dosed according to center's standard of care. At 3-5 months post-transplant, subjects were randomized, tacrolimus was discontinued (withdrawal was to be completed within 2 weeks [maximum of 4 weeks] of sirolimus initiation) and subjects received sirolimus tablets, orally, at a dose to achieve trough levels of 7-15 nanograms per milliliter (ng/mL) during the first year post-transplant, then 5-15 ng/mL. subjects remained on an inosine monophosphate dehydrogenase (IMPDH) inhibitor (mycophenolate mofetil [MMF] or mycophenolate sodium [MPS]; switching between the two was permitted). Corticosteroids were maintained at a minimum of 2.5 milligrams per day (mg/day) of prednisone (or equivalent); withdrawal was prohibited after randomization. subjects received study drug during the post-randomization period for up to a maximum of 18 months post-transplant.

Serious adverse events	Tacrolimus	Sirolimus	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 123 (30.89%)	50 / 131 (38.17%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	3 / 123 (2.44%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of unknown primary site			

subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma	Additional description: SAE captured in Clinical database and death in Argus. In Argus, death occurred due to "Squamous cell carcinoma of the tongue", which was reported as "metastatic squamous cell carcinoma" in Clinical and, used for capturing death in disclosure draft.		
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metastatic uterine cancer			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	4 / 123 (3.25%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 123 (0.81%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granuloma			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 123 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudopolyp			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 123 (0.81%)	4 / 131 (3.05%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			

Anaphylactic reaction			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	1 / 123 (0.81%)	3 / 131 (2.29%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	1 / 123 (0.81%)	11 / 131 (8.40%)	
occurrences causally related to treatment / all	0 / 1	5 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			

subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 123 (0.81%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunosuppressant drug level			

increased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 123 (0.81%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft dysfunction			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (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			
Anaemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 123 (0.81%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia			

subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 123 (1.63%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis ulcerative			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal artery stenosis			
subjects affected / exposed	0 / 123 (0.00%)	3 / 131 (2.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst ruptured			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 123 (0.81%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 123 (1.63%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteric reflux			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism tertiary			
subjects affected / exposed	2 / 123 (1.63%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Flank pain			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 123 (0.81%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 123 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 123 (0.81%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis bacterial			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 123 (2.44%)	6 / 131 (4.58%)	
occurrences causally related to treatment / all	3 / 3	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cryptococcal			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyomavirus-associated nephropathy			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 123 (0.81%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 123 (1.63%)	5 / 131 (3.82%)	
occurrences causally related to treatment / all	1 / 2	2 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	2 / 123 (1.63%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 123 (0.81%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 123 (0.81%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 131 (0.76%)	
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	Sirolimus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 123 (71.54%)	116 / 131 (88.55%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 123 (8.94%)	11 / 131 (8.40%)	
occurrences (all)	11	12	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	9 / 123 (7.32%)	25 / 131 (19.08%)	
occurrences (all)	10	29	
Pyrexia			

subjects affected / exposed	6 / 123 (4.88%)	13 / 131 (9.92%)	
occurrences (all)	6	22	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	5 / 123 (4.07%)	4 / 131 (3.05%)	
occurrences (all)	5	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 123 (4.88%)	9 / 131 (6.87%)	
occurrences (all)	6	9	
Oropharyngeal pain			
subjects affected / exposed	3 / 123 (2.44%)	7 / 131 (5.34%)	
occurrences (all)	3	10	
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 123 (4.07%)	8 / 131 (6.11%)	
occurrences (all)	5	8	
Weight increased			
subjects affected / exposed	4 / 123 (3.25%)	7 / 131 (5.34%)	
occurrences (all)	5	7	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 123 (5.69%)	16 / 131 (12.21%)	
occurrences (all)	8	20	
Tremor			
subjects affected / exposed	8 / 123 (6.50%)	0 / 131 (0.00%)	
occurrences (all)	8	0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	9 / 123 (7.32%)	11 / 131 (8.40%)	
occurrences (all)	10	11	
Polycythaemia			
subjects affected / exposed	7 / 123 (5.69%)	2 / 131 (1.53%)	
occurrences (all)	7	3	
Gastrointestinal disorders			

Aphthous stomatitis			
subjects affected / exposed	1 / 123 (0.81%)	13 / 131 (9.92%)	
occurrences (all)	1	17	
Diarrhoea			
subjects affected / exposed	12 / 123 (9.76%)	22 / 131 (16.79%)	
occurrences (all)	16	24	
Mouth ulceration			
subjects affected / exposed	0 / 123 (0.00%)	16 / 131 (12.21%)	
occurrences (all)	0	18	
Nausea			
subjects affected / exposed	9 / 123 (7.32%)	7 / 131 (5.34%)	
occurrences (all)	10	7	
Stomatitis			
subjects affected / exposed	1 / 123 (0.81%)	11 / 131 (8.40%)	
occurrences (all)	1	13	
Vomiting			
subjects affected / exposed	7 / 123 (5.69%)	4 / 131 (3.05%)	
occurrences (all)	10	4	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 123 (0.81%)	19 / 131 (14.50%)	
occurrences (all)	1	22	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 123 (1.63%)	19 / 131 (14.50%)	
occurrences (all)	2	22	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	9 / 123 (7.32%)	6 / 131 (4.58%)	
occurrences (all)	10	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 123 (4.88%)	7 / 131 (5.34%)	
occurrences (all)	8	8	
Upper respiratory tract infection			

subjects affected / exposed	13 / 123 (10.57%)	22 / 131 (16.79%)	
occurrences (all)	13	24	
Urinary tract infection			
subjects affected / exposed	8 / 123 (6.50%)	14 / 131 (10.69%)	
occurrences (all)	10	21	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	3 / 123 (2.44%)	15 / 131 (11.45%)	
occurrences (all)	3	17	
Hypercholesterolaemia			
subjects affected / exposed	2 / 123 (1.63%)	7 / 131 (5.34%)	
occurrences (all)	2	7	
Hyperglycaemia			
subjects affected / exposed	1 / 123 (0.81%)	8 / 131 (6.11%)	
occurrences (all)	1	9	
Hyperlipidaemia			
subjects affected / exposed	4 / 123 (3.25%)	14 / 131 (10.69%)	
occurrences (all)	4	16	
Hypokalaemia			
subjects affected / exposed	1 / 123 (0.81%)	8 / 131 (6.11%)	
occurrences (all)	1	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2009	Subjects with known allergy to iothalamate or any of its components were excluded from the study because subjects in this trial were required to receive subcutaneous injection of iothalamate for measured renal clearance.
22 April 2010	1. Instructions for iothalamate testing were added in the protocol. 2. To in line with current clinical practice, updated requirement for PCP prophylaxis to specify that all subjects must have received PCP prophylaxis for 6 months post-transplantation. 3.Clarified requirement for CMV prophylaxis to specify that subjects should have received prophylaxis for CMV infection according to local standard of care.
24 February 2011	1. Total bilirubin test was added to the blood chemistry profile to be collected at Visits 4, 5, 9, 10, 12, 14, 16 and 98. In addition, any subjects with suspected drug-induced liver injury should have had the following tests performed: albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR), and alkaline phosphatase. 2. Replaced the AE reporting sections of the protocol to reflect Pfizer requirements.
12 December 2011	1. Revisions were made to change the terminology regarding project specific events that should have been handled as SAEs. 2. Clarified that drug abuse and drug dependency were to be considered AEs and not only signs and symptoms resulting from these. 3. Clarifications were made to SAE reporting requirements throughout the protocol to align with "US Food and Drug Administration Final Rule:" Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans' dated September 2010 and the European Union "CT-3" guidance dated July 2011: Communication from the Commission Detailed Guidance on the Collection, Verification and Presentation of Adverse Event/Reaction Reports Arising From Clinical Trials on Medicinal Products for Human Use. 4. The criteria for further evaluation for subjects who presented with laboratory abnormalities that might be potentially associated with potential drug-induced liver injury were rewritten to provide greater clarity. The recommended list of repeated laboratory tests was updated to include prothrombin time (PT). 5. Clarified that generally the facts (evidence) or arguments to suggest a causal relationship with an AE should have been provided by the investigator to align with CT-3 guidance. 6. Added a new section to clarify the need for immediate notification if there was a clinical hold or similar issue taken for purposes of safety so that the sponsor was able to fulfill its reporting obligations in accordance with local legislation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported