Clinical trial results:
A 2-arm, prospective, randomized, controlled, open-label, 12 month Phase III trial to evaluate the efficacy regarding renal function of everolimus in combination with a centre specific standard immunosuppressive regimen consisting of CNI, purinantagonists and steroids versus a standard triple immunosuppressive regimen in lung transplant recipients.

Summary

EudraCT number	2011-001539-21
Trial protocol	DE
Global end of trial date	05 January 2017

Results information

Result version number	v1 (current)
This version publication date	31 December 2017
First version publication date	31 December 2017

Trial information

Trial identification

Sponsor protocol code	CRAD001ADE36

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01404325
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	05 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that an everolimus-based, quadruple immunosuppressive regimen had superior efficacy on renal function compared with a calcineurin inhibitor (CNI)-based triple immunosuppressive regimen as measured by calculated GFR (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at 12 months after randomization in lung transplant recipients.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 130
Worldwide total number of subjects	130
EEA total number of subjects	130

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)	121
From 65 to 84 years	9

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

232 patients who were de novo lung transplant recipients were planned for enrolling into the study. A total of 130 patients were actually randomized with 67 patients randomized to the quadruple low-level treatment arm and 63 patients randomized to the center-specific triple treatment arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Quadruple low level IS regimen

Arm description:

quadruple immunosuppressive (IS) regimen consisting of everolimus, CNI, MPA and steroids

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	Certican
Pharmaceutical forms	Tablet, Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus (0.25mg, 0.5mg, 0.75mg or 1.0mg) oral tablets or (0.1mg) oral dispersible tablets administered as a suspension daily dosing according to blood levels serum trough level: 4 +/- 1 ng/mL

Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	Sandimmun® Optoral
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Cyclosporine A (10 mg, 25 mg, 50 mg or 100 mg) oral capsules daily dosing according to blood levels serum trough level: 50 +/- 25 ng/mL

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

Dosage and administration details:

Tacrolimus (0.5 mg, 1 mg or 5 mg,) oral capsules as a suspension daily dosing according to blood levels serum trough level: 3-5 ng/mL

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

Dosage and administration details:	
Mycophenolate mofetil 250mg oral capsule or 500mg oral tablets daily dosing max 2000 mg/day	
Investigational medicinal product name	Mycophenolic acid
Investigational medicinal product code	
Other name	Myfortic
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Mycophenolic acid 180mg or 360mg oral tablets daily dosing max 1440 mg/day	
Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	Imurek
Pharmaceutical forms	Tablet, Powder and solvent for concentrate for solution for infusion
Routes of administration	Oral use
Dosage and administration details:	
Azathioprine 25mg or 50mg oral tablets daily or 50mg powder for infusion dosing max 2mg/kg/day	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Prednisone oral tablets daily dosing ≤ 0.15 mg/kg	
Arm title	Centre specific triple IS regimen
Arm description:	
centre specific CNI-based triple drug immunosuppression (IS)	
Arm type	Active comparator
Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	Sandimmun® Optoral
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Cyclosporine A (10 mg, 25 mg, 50 mg or 100 mg) oral capsules daily dosing according to blood levels serum trough level: ≥ 100 ng/mL	
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Tacrolimus (0.5 mg, 1 mg or 5 mg,) oral capsules as a suspension daily dosing according to blood levels serum trough level: > 5 ng/mL	
Investigational medicinal product name	Mycophenolate mofetil (MMF)
Investigational medicinal product code	
Other name	CellCept
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details:	
Mycophenolate mofetil 250mg oral capsule or 500mg oral tablets daily dosing max 2000 mg/day dosage was center-specific	

Investigational medicinal product name	Mycophenolic acid
Investigational medicinal product code	
Other name	Myfortic
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Mycophenolic acid 180mg or 360mg oral tablets daily dosing max 1440 mg/day dosage was center-specific

Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	Imurek
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion, Tablet
Routes of administration	Oral use

Dosage and administration details:

Azathioprine 25mg or 50mg oral tablets daily or 50mg powder for infusion dosing max 2mg/kg/day dosage was center-specific

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone oral tablets daily dosing ≤ 0.2 mg/kg

Number of subjects in period 1	Quadruple low level IS regimen	Centre specific triple IS regimen
Started	67	63
Completed	63	61
Not completed	4	2
Adverse event, serious fatal	2	-
non-specified reason	-	2
Graft loss/Retransplantation	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Quadruple low level IS regimen
Reporting group description: quadruple immunosuppressive (IS) regimen consisting of everolimus, CNI, MPA and steroids	
Reporting group title	Centre specific triple IS regimen
Reporting group description: centre specific CNI-based triple drug immunosuppression (IS)	

Reporting group values	Quadruple low level IS regimen	Centre specific triple IS regimen	Total
Number of subjects	67	63	130
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	64	57	121
From 65-84 years	3	6	9
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	53.9	54.2	
standard deviation	± 9.5	± 9.2	-
Gender, Male/Female Units: Subjects			
Female	27	22	49
Male	40	41	81

End points

End points reporting groups

Reporting group title	Quadruple low level IS regimen
Reporting group description: quadruple immunosuppressive (IS) regimen consisting of everolimus, CNI, MPA and steroids	
Reporting group title	Centre specific triple IS regimen
Reporting group description: centre specific CNI-based triple drug immunosuppression (IS)	

Primary: Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at 12 months

End point title	Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at 12 months
End point description: Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at 12 months The CKD-EPI equation, expressed as a single equation, is GFR = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)^-1.209 × 0.993Age × 1.018 (if female) × 1.159 (if black), where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1	
End point type	Primary
End point timeframe: Month 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mL/min				
least squares mean (confidence interval 95%)	64.5 (59.4 to 69.6)	54.6 (49.5 to 59.7)		

Statistical analyses

Statistical analysis title	cGFR according to CKD EPI at 12 months
Comparison groups	Centre specific triple IS regimen v Quadruple low level IS regimen
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at Month 1, 3, 6, 9, 12

End point title	Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at Month 1, 3, 6, 9, 12

End point description:

Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at Month 1, 3, 6, 9 and 12. The CKD-EPI equation, expressed as a single equation, is GFR = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)^-1.209 × 0.993Age × 1.018 (if female) × 1.159 (if black), where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1

End point type	Secondary

End point timeframe:

Month 1, 3, 6, 9, 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mL/min				
arithmetic mean (standard deviation)				
Month 1	73.5 (± 13.9)	67.1 (± 12.4)		
Month 3	70.4 (± 13.3)	64.3 (± 12.7)		
Month 6	69.2 (± 15.5)	63.1 (± 15.0)		
Month 9	69.0 (± 16.3)	62.3 (± 14.8)		
Month 12	68.3 (± 16.3)	61.2 (± 14.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Calculated Glomerular Filtration Rate (cGFR) according to Cystatin C-based Hoek's formula at Month 1, 3, 6, 9, 12

End point title	Calculated Glomerular Filtration Rate (cGFR) according to Cystatin C-based Hoek's formula at Month 1, 3, 6, 9, 12

End point description:

Calculated Glomerular Filtration Rate (cGFR) according to Cystatin C-based Hoek's formula at Month 1, 3, 6, 9, 12

End point type	Secondary

End point timeframe:

Month 1, 3, 6, 9, 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mL/min				
arithmetic mean (standard deviation)				
Month 1	68.5 (± 14.6)	61.8 (± 12.8)		
Month 3	65.7 (± 15.2)	60.3 (± 10.6)		
Month 6	63.0 (± 15.1)	58.7 (± 12.2)		
Month 9	61.8 (± 14.1)	57.7 (± 12.8)		
Month 12	60.8 (± 14.2)	57.5 (± 14.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 1, 3, 6, 9, 12

End point title	Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 1, 3, 6, 9, 12

End point description:

Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 1, 3, 6, 9, 12 cGFR (in mL/min/1.73 m2) = 186.3*(C-1.154)*(A-0.203)*G*R where C = the serum concentration of creatinine (mg/dL), A = age (years), G = 0.742 when gender is female, otherwise G = 1, R = 1.21 when race is black, otherwise R = 1.

End point type	Secondary

End point timeframe:

Month 1, 3, 6, 9, 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mL/min				
arithmetic mean (standard deviation)				
Month 1	72.0 (± 13.5)	65.8 (± 11.8)		
Month 3	68.7 (± 12.2)	63.3 (± 12.3)		
Month 6	67.6 (± 14.1)	62.3 (± 15.0)		
Month 9	67.4 (± 14.9)	61.7 (± 15.1)		
Month 12	67.0 (± 14.8)	60.5 (± 14.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 1, 3, 6, 9, 12

End point title	Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 1, 3, 6, 9, 12

End point description:

Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 1, 3, 6, 9, 12 For men: GFR=(140 -Age) x Body weight[kg] / 72 x Serum Creatinine [mg/dl] For women: GFR=0.85 (140 -Age) x Body weight[kg] / 72 x Serum Creatinine [mg/dl]

End point type	Secondary

End point timeframe:

Month 1, 3, 6, 9, 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mL/min				
arithmetic mean (standard deviation)				
Month 1	78.6 (± 19.2)	72.1 (± 14.9)		
Month 3	76.1 (± 17.6)	70.1 (± 16.0)		
Month 6	76.2 (± 19.3)	69.1 (± 17.5)		
Month 9	76.2 (± 20.1)	69.0 (± 18.2)		
Month 12	76.2 (± 20.6)	68.4 (± 17.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of patients experiencing a decline in GFR of < 10, 10-15, 15-20, 20-25 and > 25 mL/min from Baseline to Month 6 and 12.

End point title	Incidence of patients experiencing a decline in GFR of < 10, 10-15, 15-20, 20-25 and > 25 mL/min from Baseline to Month 6 and 12.

End point description:

Incidence of patients experiencing a decline in GFR of < 10, 10-15, 15-20, 20-25 and > 25 mL/min from Baseline to Month 6 and 12calculated by the CKD-EPI method. Participants are counted in each decline level observed for that participant; this means participants may be counted in more than 1 decline level.

End point type	Secondary

End point timeframe:

Baseline, Month 6, Month 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: count of incidences				
Up to Month 6: < 10 mL/min	28	44		
Up to Month 6: 10 - < 15 mL/min	9	18		
Up to Month 6: 15 - < 20 mL/min	6	11		
Up to Month 6: 20 - < 25 mL/min	2	7		
Up to Month 6: > 25 mL/min	3	7		
Up to Month 12: < 10 mL/min	36	53		
Up to Month 12: 10 - < 15 mL/min	10	27		
Up to Month 12: 15 - < 20 mL/min	8	18		
Up to Month 12: 20 - < 25 mL/min	8	9		
Up to Month 12: > 25 mL/min	7	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of renal replacement therapy at Month 6 and Month 12

End point title	Incidence of renal replacement therapy at Month 6 and Month 12

End point description:

Incidence of renal replacement therapy at Month 6 and Month 12: There were no incidences in either group where renal replacement therapy was required

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: count of incidences				
up to Month 6	0	0		
up to Month 12	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to renal replacement therapy at Month 6 and Month 12

End point title	Time to renal replacement therapy at Month 6 and Month 12

End point description:

Time to renal replacement therapy at Month 6 and Month 12: There were no incidences in either group where renal replacement therapy was required

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: days				

Notes:

[1] - There were no incidences in either group where renal replacement therapy was required

[2] - There were no incidences in either group where renal replacement therapy was required

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of acute rejection episodes at Month 6 and Month 12

End point title	Incidence of acute rejection episodes at Month 6 and Month 12

End point description:

Incidence of acute rejection episodes at Month 6 and Month 12. This table counts multiple occurrences of rejection in the same patient as different incidents. Every incident is associated with both an A and a B classification.

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: count of incidences				
Up to 6 months: Classification A	11	13		
Up to 6 months: Classification B	11	13		
6 to 12 months: Classification A	10	9		
6 to 12 months: Classification B	10	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of graft loss/re-transplantation at Month 6 and Month 12

End point title	Incidence of graft loss/re-transplantation at Month 6 and Month 12
End point description:	
Incidence of graft loss/re-transplantation at Month 6 and Month 12	
End point type	Secondary
End point timeframe:	
Month 6, Month 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: count of incidences				
Month 6	0	0		
Month 12	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Bronchiolitis obliterans syndrome (BOS) at Month 6 and Month 12

End point title	Incidence of Bronchiolitis obliterans syndrome (BOS) at Month 6 and Month 12
End point description:	
Incidence of Bronchiolitis obliterans syndrome (BOS) at Month 6 and Month 12	
End point type	Secondary
End point timeframe:	
Month 6, Month 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: count of incidences				
Month 6 - Total (all grades)	66	61		
Month 12 - Total (all grades)	66	61		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of death at Month 6 and Month 12

End point title	Incidence of death at Month 6 and Month 12
End point description:	
Incidence of death at Month 6 and Month 12	
End point type	Secondary
End point timeframe:	
Month 6, Month 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: number of events				
Month 6	0	0		
Month 12	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (QoL, SF36) at Month 6 and Month 12

End point title	Quality of Life (QoL, SF36) at Month 6 and Month 12
End point description:	
Quality of Life (QoL, SF36) at Month 6 and Month 12 Scores can range from a minimum of 0 (maximum disability) to a maximum of 100 (no disability).	
End point type	Secondary
End point timeframe:	
Month 6, Month 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: score				
arithmetic mean (standard deviation)				
Month 6: Physical component summary score	46.9 (± 7.6)	48.9 (± 7.3)		
Month 6: Mental component summary score	51.5 (± 10.8)	52.6 (± 8.1)		
Month 6: Physical functioning	78.8 (± 20.9)	84.1 (± 16.8)		
Month 6: Role-Physical	71.1 (± 23.2)	77.1 (± 24.2)		
Month 6: Bodily pain	76.4 (± 27.9)	81.3 (± 23.4)		
Month 6: General health perception	65.4 (± 19.2)	70.6 (± 19.9)		
Month 6: Vitality	67.4 (± 18.0)	70.0 (± 14.6)		
Month 6:Social functioning	84.1 (± 22.6)	88.9 (± 17.6)		
Month 6: Role-Emotional	84.7 (± 22.4)	84.8 (± 17.9)		
Month 6: Mental health	78.5 (± 17.2)	81.0 (± 12.8)		
Month 12: Physical component summary score	47.2 (± 8.8)	47.7 (± 7.1)		
Month 12: Mental component summary score	49.7 (± 11.8)	53.8 (± 9.1)		
Month 12: Physical functioning	77.4 (± 21.8)	82.5 (± 20.0)		
Month 12: Role-Physical	68.3 (± 26.8)	78.0 (± 22.9)		
Month 12: Bodily Pain	76.8 (± 27.0)	80.1 (± 22.7)		
Month 12: General health perception	66.7 (± 17.3)	65.8 (± 20.3)		
Month 12: Vitality	65.7 (± 19.4)	69.9 (± 17.5)		
Month 12: Social functioning	82.3 (± 23.0)	90.5 (± 16.1)		
Month 12: Role-Emotional	79.4 (± 27.3)	86.2 (± 20.5)		
Month 12: Mental health	75.4 (± 18.2)	81.8 (± 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exercise capacity 6-Minute walk test(6MWT) at Month 6 and Month 12

End point title	Exercise capacity 6-Minute walk test(6MWT) at Month 6 and Month 12

End point description:

Exercise capacity (6MWT) at Month 6 and Month 12 The higher the Borg score implies increased shortness of breath and/or increased fatigue.

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: Score				
arithmetic mean (standard deviation)				
Month 6-Borg score - Before start of test	0.47 (± 0.78)	0.39 (± 0.77)		
Month 6-Borg score - At end of test	1.75 (± 1.58)	1.64 (± 1.31)		
Month 12-Borg score - Before start of test	0.38 (± 0.94)	0.42 (± 0.79)		
Month 12-Borg score - At end of test	2.08 (± 1.58)	2.06 (± 1.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treated arterial hypertension up to Month 12

End point title	Incidence of treated arterial hypertension up to Month 12
End point description:	
Incidence of treated of arterial hypertension up to Month 12	
End point type	Secondary
End point timeframe:	
up to Month 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: number of event				
Month 1	2	1		
Month 3	2	1		
Month 6	2	1		
Month 9	3	1		
Month 12	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Diabetes Mellitus up to Month 12

End point title	Incidence of Diabetes Mellitus up to Month 12

End point description:

Incidence of Diabetes Mellitus up to Month 12

End point type	Secondary

End point timeframe:

up to Month 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: number of events				
Month 1	0	0		
Month 3	0	0		
Month 6	0	1		
Month 9	1	1		
Month 12	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough levels of everolimus at Month 1, 3, 6, 9, 12

End point title	Trough levels of everolimus at Month 1, 3, 6, 9, 12[3]

End point description:

Trough levels of everolimus at Month 1, 3, 6, 9, 12

End point type	Secondary

End point timeframe:

Month 1, 3, 6, 9, 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This Endpoint is on everolimus levels only

End point values	Quadruple low level IS regimen			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 1 n=66	4.2 (± 1.4)			
Month 3 n=61	4.4 (± 1.2)			
Month 6 n=58	4.1 (± 1.2)			
Month 9 n=52	4.5 (± 1.6)			

Month 12 n=50	4.3 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to target ranges of everolimus at Month 1, 3, 6, 9, 12

End point title	Adherence to target ranges of everolimus at Month 1, 3, 6, 9, 12[4]

End point description:

Adherence to target ranges of everolimus at Month 1, 3, 6, 9, 12

End point type	Secondary

End point timeframe:

Month 1, 3, 6, 9, 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This Endpoint is on everolimus levels only

End point values	Quadruple low level IS regimen			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: participant adherence				
Month 1 Below Target Range	10			
Month 1 Within Target Range	42			
Month 1 Above Target Range	14			
Month 3 Below Target Range	5			
Month 3 Within Target Range	41			
Month 3 Above Target Range	15			
Month 6 Below Target Range	7			
Month 6 Within Target Range	39			
Month 6 Above Target Range	12			
Month 9 Below Target Range	5			
Month 9 Within Target Range	34			
Month 9 Above Target Range	13			
Month 12 Below Target Range	3			
Month 12 Within Target Range	38			
Month 12 Above Target Range	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough levels of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12

End point title	Trough levels of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12
End point description:	
Trough levels of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12	
End point type	Secondary
End point timeframe:	
Month 1, 3, 6, 9, 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 1 n=21, 16	61 (± 21.83)	106 (± 21.25)		
Month 3 n=20, 14	59.65 (± 20.43)	109 (± 24.95)		
Month 6 n= 20, 14	58.50 (± 12.84)	103 (± 32.95)		
Month 9 n=17, 13	57.59 (± 23.26)	107 (± 29.13)		
Month 12 n=21, 13	69.33 (± 48.41)	108 (± 27.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to target ranges of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12

End point title	Adherence to target ranges of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12
End point description:	
Adherence to target ranges of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12	
End point type	Secondary
End point timeframe:	
Month 1, 3, 6, 9, 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: participant adherence				
Month 1 Below Target Range	0	8		
Month 1 Within Target Range	18	8		

Month 1 Above Target Range	3	0		
Month 3 Below Target Range	0	4		
Month 3 Within Target Range	18	10		
Month 3 Above Target Range	2	0		
Month 6 Below Target Range	0	6		
Month 6 Within Target Range	18	8		
Month 6 Above Target Range	2	0		
Month 9 Below Target Range	0	4		
Month 9 Within Target Range	16	9		
Month 9 Above Target Range	1	0		
Month 12 Below Target Range	0	3		
Month 12 Within Target Range	16	10		
Month 12 Above Target Range	5	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough levels of Tacrolimus at Month 1, 3, 6, 9, 12

End point title	Trough levels of Tacrolimus at Month 1, 3, 6, 9, 12
End point description: Trough levels of Tacrolimus at Month 1, 3, 6, 9, 12	
End point type	Secondary
End point timeframe: Month 1, 3, 6, 9, 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 1 n=44, 45	5.07 (± 1.80)	10.44 (± 2.73)		
Month 3 n=44, 47	5.18 (± 2.02)	10.53 (± 2.88)		
Month 6 n= 40, 46	4.70 (± 1.98)	10.09 (± 3.37)		
Month 9 n=38, 46	5.78 (± 4.18)	10.67 (± 3.44)		
Month 12 n=41, 47	5.19 (± 2.36)	9.66 (± 3.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to target ranges of Tacrolimus at Month 1, 3, 6, 9, 12

End point title	Adherence to target ranges of Tacrolimus at Month 1, 3, 6, 9, 12

End point description:

Adherence to target ranges of Tacrolimus at Month 1, 3, 6, 9, 12

End point type	Secondary

End point timeframe:

Month 1, 3, 6, 9, 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: participant adherence				
Month 1 Below Target Range	3	0		
Month 1 Within Target Range	24	45		
Month 1 Above Target Range	17	0		
Month 3 Below Target Range	3	0		
Month 3 Within Target Range	23	47		
Month 3 Above Target Range	18	0		
Month 6 Below Target Range	5	1		
Month 6 Within Target Range	23	45		
Month 6 Above Target Range	12	0		
Month 9 Below Target Range	2	0		
Month 9 Within Target Range	18	46		
Month 9 Above Target Range	18	0		
Month 12 Below Target Range	3	0		
Month 12 Within Target Range	23	47		
Month 12 Above Target Range	15	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of bacterial, viral, and fungal infections at Month 12

End point title	Incidence of bacterial, viral, and fungal infections at Month 12

End point description:

Incidence of bacterial, viral, and fungal infections at Month 12

End point type	Secondary

End point timeframe:

Month 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: number of incidences				
Bacterial infections	3	4		
Viral infections	14	20		
Fungal infections	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Triglyceride levels at Month 1, 3, 6, 9, 12

End point title	Triglyceride levels at Month 1, 3, 6, 9, 12
End point description:	
Triglyceride levels at Month 1, 3, 6, 9, 12	
End point type	Secondary
End point timeframe:	
Month 1, 3, 6, 9, 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mmol/L				
arithmetic mean (standard deviation)				
Month 1 (n=66, 60)	2.6 (± 1.4)	2.0 (± 0.9)		
Month 3 (n=65, 60)	2.7 (± 1.3)	2.1 (± 1.0)		
Month 6 (n=60, 60)	2.6 (± 1.2)	2.0 (± 1.1)		
Month 9 (n=55, 59)	2.7 (± 1.3)	2.0 (± 1.0)		
Month 12 (n=63, 60)	2.7 (± 1.5)	2.1 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Cholesterol levels at Month 1, 3, 6, 9, 12

End point title	Total Cholesterol levels at Month 1, 3, 6, 9, 12
End point description:	
Total Cholesterol levels at Month 1, 3, 6, 9, 12	
End point type	Secondary

End point timeframe:
Month 1, 3, 6, 9, 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mmol/L				
arithmetic mean (standard deviation)				
Month 1 (n=64, 60)	0.8 (± 0.8)	-0.2 (± 0.7)		
Month 3 (n=63, 60)	1.0 (± 0.8)	-0.1 (± 0.9)		
Month 6 (n=59, 60)	1.1 (± 0.9)	-0.2 (± 0.8)		
Month 9 (n=54, 59)	1.1 (± 0.9)	-0.1 (± 0.9)		
Month 12 (n=61, 60)	0.8 (± 1.1)	-0.1 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Low-Density Lipoprotein (LDL)Cholesterol levels at Month 1, 3, 6, 9, 12

End point title	Low-Density Lipoprotein (LDL)Cholesterol levels at Month 1, 3, 6, 9, 12
End point description: LDL Cholesterol levels at Month 1, 3, 6, 9, 12	
End point type	Secondary
End point timeframe: Month 1, 3, 6, 9, 12	

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mmol/L				
arithmetic mean (standard deviation)				
Month 1 (n=63, 57)	0.4 (± 0.8)	0.0 (± 0.5)		
Month 3 (n=62, 58)	0.6 (± 0.7)	-0.0 (± 0.6)		
Month 6 (n=58, 57)	0.7 (± 0.8)	-0.0 (± 0.6)		
Month 9 (n=53, 56)	0.8 (± 0.8)	0.1 (± 0.7)		
Month 12 (n=57, 57)	0.5 (± 0.9)	0.1 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: High-Density Lipoprotein (HDL)Cholesterol levels at Month 1, 3, 6, 9, 12

End point title	High-Density Lipoprotein (HDL)Cholesterol levels at Month 1, 3, 6, 9, 12

End point description:

HDL Cholesterol levels at Month 1, 3, 6, 9, 12

End point type	Secondary

End point timeframe:

Month 1, 3, 6, 9, 12

End point values	Quadruple low level IS regimen	Centre specific triple IS regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: mmol/L				
arithmetic mean (standard deviation)				
Month 1 (n=65, 59)	0.1 (± 0.3)	-0.1 (± 0.3)		
Month 3 (n=64, 59)	0.1 (± 0.3)	-0.0 (± 0.4)		
Month 6 (n=60, 59)	0.1 (± 0.4)	-0.0 (± 0.4)		
Month 9 (n=55, 58)	0.0 (± 0.4)	-0.0 (± 0.4)		
Month 12 (n=59, 59)	0.0 (± 0.5)	-0.0 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Center specific triple IS
Reporting group description:	
Center specific triple IS	
Reporting group title	Quadruple low level IS
Reporting group description:	
Quadruple low level IS	

Serious adverse events	Center specific triple IS	Quadruple low level IS	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 63 (34.92%)	29 / 67 (43.28%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BLADDER TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

LYMPHOCELE			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHORRHOEA			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL VENOUS DISEASE			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	0 / 63 (0.00%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHILLS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERNIA			
subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLAMMATION			

subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCAL SWELLING			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALISED OEDEMA			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
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 / 63 (0.00%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	3 / 63 (4.76%)	4 / 67 (5.97%)	
occurrences causally related to treatment / all	2 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
LUNG TRANSPLANT REJECTION			
subjects affected / exposed	0 / 63 (0.00%)	5 / 67 (7.46%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 63 (0.00%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
BRONCHOSTENOSIS			
subjects affected / exposed	2 / 63 (3.17%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	4 / 63 (6.35%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IDIOPATHIC PULMONARY FIBROSIS			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFILTRATION			
subjects affected / exposed	0 / 63 (0.00%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

OBLITERATIVE BRONCHIOLITIS			
subjects affected / exposed	1 / 63 (1.59%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORGANISING PNEUMONIA			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAINFUL RESPIRATION			
subjects affected / exposed	0 / 63 (0.00%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 63 (3.17%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SLEEP APNOEA SYNDROME			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

FORCED EXPIRATORY VOLUME DECREASED			
subjects affected / exposed	5 / 63 (7.94%)	9 / 67 (13.43%)	
occurrences causally related to treatment / all	4 / 8	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMMUNOSUPPRESSANT DRUG LEVEL INCREASED			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY FUNCTION TEST DECREASED			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
COMPLICATIONS OF TRANSPLANTED LUNG			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MATERNAL EXPOSURE DURING PREGNANCY			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
HYDROCELE			

subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COR PULMONALE			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 63 (0.00%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS TACHYCARDIA			

subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (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			
HEADACHE			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAPARESIS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TREMOR			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
LEUKOPENIA			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
RETINAL DETACHMENT			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL VEIN OCCLUSION			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	2 / 63 (3.17%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGIC EROSIVE GASTRITIS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
NIGHT SWEATS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URGE INCONTINENCE			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
PSEUDARTHROSIS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ATYPICAL PNEUMONIA			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	1 / 63 (1.59%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS BACTERIAL			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS VIRAL			

subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	4 / 63 (6.35%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	2 / 63 (3.17%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	1 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	3 / 63 (4.76%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 3	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA VIRAL			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			

subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 63 (4.76%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPERINFECTION BACTERIAL			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRACHEOBRONCHITIS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			

subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Center specific triple IS	Quadruple low level IS	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 63 (92.06%)	62 / 67 (92.54%)	
Investigations			
BRONCHOALVEOLAR LAVAGE ABNORMAL			
subjects affected / exposed	6 / 63 (9.52%)	3 / 67 (4.48%)	
occurrences (all)	6	3	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	4 / 63 (6.35%)	2 / 67 (2.99%)	
occurrences (all)	4	3	
FORCED EXPIRATORY VOLUME DECREASED			
subjects affected / exposed	8 / 63 (12.70%)	7 / 67 (10.45%)	
occurrences (all)	8	7	
PULMONARY FUNCTION TEST DECREASED			
subjects affected / exposed	3 / 63 (4.76%)	6 / 67 (8.96%)	
occurrences (all)	4	7	
Injury, poisoning and procedural complications			
COMPLICATIONS OF TRANSPLANTED LUNG			
subjects affected / exposed	4 / 63 (6.35%)	0 / 67 (0.00%)	
occurrences (all)	4	0	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	4 / 63 (6.35%)	7 / 67 (10.45%)	
occurrences (all)	4	7	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	9 / 63 (14.29%)	8 / 67 (11.94%)	
occurrences (all)	11	8	

MIGRAINE			
subjects affected / exposed	4 / 63 (6.35%)	3 / 67 (4.48%)	
occurrences (all)	7	4	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 63 (4.76%)	6 / 67 (8.96%)	
occurrences (all)	3	6	
LEUKOPENIA			
subjects affected / exposed	19 / 63 (30.16%)	15 / 67 (22.39%)	
occurrences (all)	25	18	
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	5 / 63 (7.94%)	2 / 67 (2.99%)	
occurrences (all)	5	2	
OEDEMA PERIPHERAL			
subjects affected / exposed	10 / 63 (15.87%)	19 / 67 (28.36%)	
occurrences (all)	11	20	
PYREXIA			
subjects affected / exposed	5 / 63 (7.94%)	1 / 67 (1.49%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	10 / 63 (15.87%)	9 / 67 (13.43%)	
occurrences (all)	12	10	
NAUSEA			
subjects affected / exposed	10 / 63 (15.87%)	9 / 67 (13.43%)	
occurrences (all)	14	10	
VOMITING			
subjects affected / exposed	4 / 63 (6.35%)	5 / 67 (7.46%)	
occurrences (all)	8	5	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	7 / 63 (11.11%)	10 / 67 (14.93%)	
occurrences (all)	7	11	
OROPHARYNGEAL PAIN			

subjects affected / exposed	4 / 63 (6.35%)	4 / 67 (5.97%)	
occurrences (all)	4	4	
PRODUCTIVE COUGH			
subjects affected / exposed	5 / 63 (7.94%)	1 / 67 (1.49%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	1 / 63 (1.59%)	12 / 67 (17.91%)	
occurrences (all)	1	14	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	5 / 63 (7.94%)	2 / 67 (2.99%)	
occurrences (all)	5	2	
BACK PAIN			
subjects affected / exposed	5 / 63 (7.94%)	2 / 67 (2.99%)	
occurrences (all)	5	3	
PAIN IN EXTREMITY			
subjects affected / exposed	5 / 63 (7.94%)	8 / 67 (11.94%)	
occurrences (all)	5	8	
Infections and infestations			
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	11 / 63 (17.46%)	10 / 67 (14.93%)	
occurrences (all)	16	14	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 63 (6.35%)	2 / 67 (2.99%)	
occurrences (all)	5	2	
NASOPHARYNGITIS			
subjects affected / exposed	17 / 63 (26.98%)	17 / 67 (25.37%)	
occurrences (all)	21	20	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	7 / 63 (11.11%)	8 / 67 (11.94%)	
occurrences (all)	10	10	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 63 (3.17%)	4 / 67 (5.97%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2011	Amendment 1: (prior to study start), introduced the following change: Clarification of the involvement of a CRO.
01 August 2012	Amendment 2: introduced the following changes: 1) Clarified that 1 measurement of the GFR by CKD EPI prior to screening and baseline visit was sufficient, rather than 2 measurements. 2) Tablets for preparation of a suspension, containing 0.1 mg everolimus, were allowed as study medication. 3) 1 spirometry assessment could be skipped at either screening or baseline visit when the visits occurred within 5 days of each other.
30 January 2015	Amendment 3: introduced the following changes: 1) Out of 3 scheduled GFR measurements (CKD-EPI), i.e. 1 prior screening (d-42 to d-1 before screening) 1 at screening (d -42 to d-1) and 1 at baseline (d1), all of these 3 measurements needed to be ≥ 40 mL/min and ≤ 100 mL/min/1.73 m2; however, 1 measurement out of these 3 with at least ≥ 50 mL/min/1.73 m2 and ≤ 90 mL/min/1.73m2 was sufficient to qualify for eligibility with respect to this criterion 2) Allowance of CsA trough level reduction once patients reached 2 years post-transplant 3) Trade names of 'other immunosuppressive drugs' were changed to generic names 4) Corrections of typos for clarification.
25 November 2015	Amendment 4: introduced the following change: Enrollment was to be terminated by 31-Dec-2015 due to slow recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported