



Clinical trial results:

A Clinical Study to Evaluate the Efficacy and Safety of Cyclosporine (CsA) and Sirolimus (SRL) Induction Followed by Cyclosporine Withdrawal in Korean Renal Allograft Recipients

Summary

EudraCT number	2014-004101-33
Trial protocol	Outside EU/EEA
Global end of trial date	11 November 2008

Results information

Result version number	v1 (current)
This version publication date	21 June 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	0468E-102362
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00478608
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: B1741076

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	ClinicalTrials.gov_Inquiries@pfizer.com , Pfizer Inc, 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	ClinicalTrials.gov_Inquiries@pfizer.com , Pfizer Inc, 001 8007181021, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 November 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of sirolimus assessed by the incidence of biopsy-confirmed acute rejection episode at 6 months after transplantation in Korean renal transplantation recipients.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 79
Worldwide total number of subjects	79
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	22
Adults (18-64 years)	57
From 65 to 84 years	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited in Korea from March 2007 to November 2007.

Pre-assignment

Screening details:

Subjects were screened up to 7 days.

Period 1

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

Arms

Arm title	Sirolimus (SRL)
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Arm description:

Subjects initially received SRL, Cyclosporine (CsA) and Corticosteroids (CS). 2-4 months following transplantation (trans), CsA was progressively withdrawn. On Day 1 (within 48 hours after trans) SRL was initiated (6 milligram (mg) loading dose). For Day 2 through CsA withdrawal (w/d), SRL dose was 2 milligram per day (mg/day), with adjustment to maintain a target trough blood level of 5-15 nanogram per millilitre (ng/ml). During CsA w/d through month 6, SRL dose adjusted to a trough level of 15-30 ng/ml; and for months 7-12, a trough level of 12-24 ng/ml. CsA initiated before or within 48 hours after trans at a dose to attain a trough level of 200-400 ng/ml. From month 1 to time of CsA w/d, CsA dose was adjusted to maintain a trough level of 150-300 ng/ml. 2-4 months after trans, CsA was withdrawn over 4-8 weeks. CS were initiated within 24 hours before or after trans and tapered to greater than or equal to (\geq) 5 mg/day of prednisone by the end of week 13. W/d of cs was prohibited.

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

Dosage and administration details:

SRL was administered at a loading dose of 6 mg on day 1, 2 mg on day 2 and adjusted to trough level of 5-15 ng/mL.

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

Dosage and administration details:

On month one CsA dose was adjusted to attain trough level of 200 - 400 ng/mL. From month one to CsA withdrawal the CsA dose was adjusted to attain trough level of 150 - 300 ng/mL.

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

Dosage and administration details:

Corticosteroids was administered at a dose of 5 mg once daily.

Number of subjects in period 1	Sirolimus (SRL)
Started	79
Completed	59
Not completed	20
Adverse Event	15
'Protocol Violation '	3
'Withdrawal by Subject '	2

Baseline characteristics

Reporting groups

Reporting group title	Sirolimus (SRL)
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Reporting group description:

Subjects initially received SRL, Cyclosporine (CsA) and Corticosteroids (CS). 2-4 months following transplantation (trans), CsA was progressively withdrawn. On Day 1 (within 48 hours after trans) SRL was initiated (6 milligram (mg) loading dose). For Day 2 through CsA withdrawal (w/d), SRL dose was 2 milligram per day (mg/day), with adjustment to maintain a target trough blood level of 5-15 nanogram per millilitre (ng/ml). During CsA w/d through month 6, SRL dose adjusted to a trough level of 15-30 ng/ml; and for months 7-12, a trough level of 12-24 ng/ml. CsA initiated before or within 48 hours after trans at a dose to attain a trough level of 200-400 ng/ml. From month 1 to time of CsA w/d, CsA dose was adjusted to maintain a trough level of 150-300 ng/ml. 2-4 months after trans, CsA was withdrawn over 4-8 weeks. CS were initiated within 24 hours before or after trans and tapered to greater than or equal to (\geq) 5 mg/day of prednisone by the end of week 13. W/d of cs was prohibited.

Reporting group values	Sirolimus (SRL)	Total	
Number of subjects	79	79	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	40.16 \pm 12.69	-	
Gender categorical Units: Subjects			
Female	47	47	
Male	32	32	

End points

End points reporting groups

Reporting group title	Sirolimus (SRL)
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Reporting group description:

Subjects initially received SRL, Cyclosporine (CsA) and Corticosteroids (CS). 2-4 months following transplantation (trans), CsA was progressively withdrawn. On Day 1 (within 48 hours after trans) SRL was initiated (6 milligram (mg) loading dose). For Day 2 through CsA withdrawal (w/d), SRL dose was 2 milligram per day (mg/day), with adjustment to maintain a target trough blood level of 5-15 nanogram per millilitre (ng/ml). During CsA w/d through month 6, SRL dose adjusted to a trough level of 15-30 ng/ml; and for months 7-12, a trough level of 12-24 ng/ml. CsA initiated before or within 48 hours after trans at a dose to attain a trough level of 200-400 ng/ml. From month 1 to time of CsA w/d, CsA dose was adjusted to maintain a trough level of 150-300 ng/ml. 2-4 months after trans, CsA was withdrawn over 4-8 weeks. CS were initiated within 24 hours before or after trans and tapered to greater than or equal to (\geq) 5 mg/day of prednisone by the end of week 13. W/d of cs was prohibited.

Primary: Number of Subjects Experiencing Biopsy Confirmed Acute Rejection Through Month 6 After Transplantation

End point title	Number of Subjects Experiencing Biopsy Confirmed Acute Rejection Through Month 6 After Transplantation ^[1]
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End point description:

The diagnosis of acute rejection required a kidney biopsy. Biopsies were assessed using the Banff criteria, standardized diagnostic categories based on histological assessments example (e.g.), cell types and distributions. Subjects who received at least one dosing of SRL after transplantation. Subjects who received at least one dosing of SRL after transplantation.

End point type	Primary
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End point timeframe:

6 months after transplantation

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be analysed for this outcome measure.

End point values	Sirolimus (SRL)			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Glomerular Filtration Rate (GFR) (Nankivell Method)

End point title	Glomerular Filtration Rate (GFR) (Nankivell Method)
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End point description:

GFR is an index of kidney function. GFR describes the flow rate of filtered fluid through the kidney. GFR can be measured directly or estimated using established formulas. For this study, GFR was calculated using the Nankivell formula. A normal GFR is >90 mL/min, although children and older people usually have a lower GFR. Lower values indicate poorer kidney function. A GFR <15 is consistent with kidney failure. Subjects who received at least one dose of SRL after transplantation. Observed values.

End point type	Secondary
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End point timeframe:

6 and 12 months

End point values	Sirolimus (SRL)			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: millilitre (mL)				
arithmetic mean (standard deviation)				
6 months	67.36 (\pm 15.25)			
12 months	71.92 (\pm 18.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Creatinine (On-Therapy Analysis)

End point title Serum Creatinine (On-Therapy Analysis)

End point description:

Serum creatinine is an indicator of kidney function. Creatinine is a substance formed from the metabolism of creatine, commonly found in blood, urine, and muscle tissue. It is removed from the blood by the kidneys and excreted in urine. An increased level of creatinine in the blood indicates decreased kidney function. Normal adult blood levels of creatinine are 0.5 to 1.1 mg/dL for females and 0.6 to 1.2 mg/dL for males; however, the normal values are age-dependent as elderly subjects typically have smaller muscle mass. Subjects who received at least one dose of SRL after transplantation.

End point type Secondary

End point timeframe:

Observed values Baseline, 6 and 12 months

End point values	Sirolimus (SRL)			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: mL/min				
arithmetic mean (standard deviation)				
Baseline	9.42 (\pm 3.64)			
6 months	1.3 (\pm 0.36)			
12 months	1.25 (\pm 0.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subject and Graft Survival

End point title	Subject and Graft Survival
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End point description:

Subject survival defined as subjects living with or without a functioning graft. Graft survival defined as those subjects who did not experience graft loss. Graft loss defined as physical loss (nephrectomy), functional loss (necessitating maintenance dialysis for > 8 weeks), retransplant or death during the first 12 months after randomization. Subjects who received at least one dosing of SRL after transplantation. Patients who received at least one dosing of SRL after transplantation.

End point type	Secondary
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End point timeframe:

12 months

End point values	Sirolimus (SRL)			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: subjects				
Subject survival 6 months	77			
Subject survival 12 months	76			
Graft survival 6 months	77			
Graft survival 12 months	76			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing Biopsy Confirmed Acute Rejection Through Month 12 After Transplantation

End point title	Number of Subjects Experiencing Biopsy Confirmed Acute Rejection Through Month 12 After Transplantation
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End point description:

The diagnosis of acute rejection required a kidney biopsy. Biopsies were assessed using the Banff criteria, standardized diagnostic categories based on histological assessments (e.g., cell types and distributions). Subjects who received at least one dosing of SRL after transplantation. Subjects who received at least one dosing of SRL after transplantation.

End point type	Secondary
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End point timeframe:

12 months after transplantation

End point values	Sirolimus (SRL)			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: subjects	15			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored through one month following discontinuation of SRL

Adverse event reporting additional description:

The same event may appear as both an AE and a 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.1
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Reporting groups

Reporting group title	Sirolimus (SRL)
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Reporting group description:

Subjects initially received SRL, Cyclosporine (CsA) and Corticosteroids. After 2-4 months following transplantation, CsA was progressively withdrawn. On Day 1 (within 48 hours after transplantation) SRL was initiated (6 mg loading dose). For Day 2 through CsA withdrawal (w/d), SRL dose was 2mg/day, with adjustment to maintain a target trough blood level of 5-15 ng/ml. During CsA w/d through month 6, SRL dose adjusted to a trough level of 15-30 ng/ml; and for months 7-12, a trough level of 12-24 ng/ml. CsA initiated before or within 48 hours after transplantation at a dose to attain a trough level of 200-400 ng/ml. From month 1 to time of CsA w/d, CsA dose was adjusted to maintain a trough level of 150-300 ng/ml. At 2 to 4 months after transplantation, CsA was withdrawn over 4-8 weeks. Corticosteroids were initiated within 24 hours before or after transplantation and tapered to ≥ 5 mg/day of prednisone by the end of week 13. W/d of corticosteroids was prohibited.

Serious adverse events	Sirolimus (SRL)		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 79 (49.37%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphocele			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences causally related to treatment / all	6 / 8		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death (unknown cause)			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asphyxia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Investigations			
Blood creatinine increased			
subjects affected / exposed	10 / 79 (12.66%)		
occurrences causally related to treatment / all	2 / 12		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood glucose increased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocarditis			

subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Faecaloma			

subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal mass			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Varicella			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Parotitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary tuberculosis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fungal infection			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Sirolimus (SRL)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 79 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	7		
Lymphocele			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 79 (10.13%)		
occurrences (all)	9		
Chest discomfort			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	6		
Generalised oedema			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Oedema			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Pitting oedema			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Face oedema			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Catheter site pain			

subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Mass subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Influenza like illness subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Swelling subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Sense of oppression subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Xerosis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Reproductive system and breast disorders			
Ovarian cyst subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Erectile dysfunction subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Genital haemorrhage subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Dysmenorrhoea			

subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Amenorrhoea subjects affected / exposed occurrences (all)	4 / 79 (5.06%) 4		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	8 / 79 (10.13%) 9		
Rhinorrhoea subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 7		
Dyspnoea subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 7		
Productive cough subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 3		
Pharyngolaryngeal pain subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Hiccups subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	12 / 79 (15.19%) 12		
Sleep disorder subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Investigations			

Blood cholesterol increased subjects affected / exposed occurrences (all)	29 / 79 (36.71%) 31		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	17 / 79 (21.52%) 18		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	12 / 79 (15.19%) 15		
Urine output decreased subjects affected / exposed occurrences (all)	11 / 79 (13.92%) 12		
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	10 / 79 (12.66%) 10		
Blood creatinine increased subjects affected / exposed occurrences (all)	9 / 79 (11.39%) 11		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	9 / 79 (11.39%) 9		
Blood triglycerides increased subjects affected / exposed occurrences (all)	8 / 79 (10.13%) 8		
Blood glucose increased subjects affected / exposed occurrences (all)	8 / 79 (10.13%) 8		
Weight increased subjects affected / exposed occurrences (all)	5 / 79 (6.33%) 5		
Blood pressure increased subjects affected / exposed occurrences (all)	4 / 79 (5.06%) 4		
Blood phosphorus decreased			

subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	3		
Haemoglobin decreased			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	3		
Blood albumin decreased			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	3		
Blood potassium increased			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Blood uric acid increased			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Body temperature increased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Blood calcium decreased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Blood calcium increased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		

White blood cells urine positive subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Injury, poisoning and procedural complications			
Procedural pain subjects affected / exposed occurrences (all)	24 / 79 (30.38%) 26		
Post procedural complication subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Postoperative wound complication subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Post procedural haemorrhage subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Femur fracture subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Cardiac disorders			
Arrhythmia subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Palpitations subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Myocardial infarction subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Angina pectoris subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Nervous system disorders			

Headache			
subjects affected / exposed	15 / 79 (18.99%)		
occurrences (all)	16		
Convulsion			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Neuropathy peripheral			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Dysarthria			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Migrane			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
neuralgia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed occurrences (all)	19 / 79 (24.05%) 19		
Leukopenia subjects affected / exposed occurrences (all)	4 / 79 (5.06%) 4		
Neutropenia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Leukocytosis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Ear and labyrinth disorders			
Hypoacusis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Ear pain subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Eye disorders			
Visual disturbance subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Vision blurred subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Xerophthalmia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Conjunctivitis			

subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Dry eye subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Eyelid oedema subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Conjunctival oedema subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	31 / 79 (39.24%) 36		
Diarrhoea subjects affected / exposed occurrences (all)	21 / 79 (26.58%) 27		
Nausea subjects affected / exposed occurrences (all)	16 / 79 (20.25%) 16		
Mouth ulceration subjects affected / exposed occurrences (all)	14 / 79 (17.72%) 15		
Vomiting subjects affected / exposed occurrences (all)	13 / 79 (16.46%) 13		
Abdominal pain subjects affected / exposed occurrences (all)	12 / 79 (15.19%) 12		
Dyspepsia subjects affected / exposed occurrences (all)	8 / 79 (10.13%) 8		
Abdominal pain upper subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 7		

Abdominal discomfort			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	6		
Stomatitis			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Abdominal distension			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Gingival hyperplasia			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Epigastric discomfort			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Haematemesis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Oral disorder			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Oral discomfort			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Faecal incontinence			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Anorectal disorder			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		

Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Hepatobiliary disorders Hepatitis subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 3		
Hepatotoxicity subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	18 / 79 (22.78%) 20		
Pruritus subjects affected / exposed occurrences (all)	10 / 79 (12.66%) 11		
Rash subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 8		
Hirsutism subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Rash papular subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 2		
Ecchymosis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 2		
Periorbital oedema subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Neurodermatitis			

subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Skin disorder subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Dry skin subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Dermal cyst subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Dermatitis acneiform subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Rash macular subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Blister subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Alopecia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Toxic skin eruption subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Swelling face subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 7		
Proteinuria subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 3		

Azotaemia subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Albuminuria subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Pollakiuria subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Renal tubular necrosis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Cushingoid subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	11 / 79 (13.92%) 11		
Arthralgia subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 6		
Musculoskeletal pain subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 3		
Myalgia subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Osteoporosis			

subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Neck pain subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Musculoskeletal discomfort subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Coccydynia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Arthritis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	26 / 79 (32.91%) 43		
Nasopharyngitis subjects affected / exposed occurrences (all)	12 / 79 (15.19%) 18		
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 7		
Herpes zoster subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 6		
Herpes simplex subjects affected / exposed occurrences (all)	4 / 79 (5.06%) 5		
Rhinitis subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		

Oral candidiasis			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Tinea versicolour			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Tinea pedis			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Varicella			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Vaginal infection			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Tinea cruris			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Bacteraemia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
BK virus infection			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Rash pustular			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		

Gingival infection subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Fungal infection subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Orchitis subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Metabolism and nutrition disorders			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	19 / 79 (24.05%) 19		
Hyperlipidaemia subjects affected / exposed occurrences (all)	12 / 79 (15.19%) 12		
Hyperkalaemia subjects affected / exposed occurrences (all)	8 / 79 (10.13%) 8		
Hypokalaemia subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 7		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	5 / 79 (6.33%) 5		
Hyperglycaemia subjects affected / exposed occurrences (all)	5 / 79 (6.33%) 5		
Diabetes mellitus subjects affected / exposed occurrences (all)	4 / 79 (5.06%) 4		
Hypophosphataemia			

subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Hypoglycaemia			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Electrolyte imbalance			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Anorexia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Hyperamylasaemia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2007	1. If the screening/baseline laboratory assessments were performed as routine examinations of the study site before the informed consent was obtained, the results of those assessment that were performed in 7 days prior to the transplantation could be acceptable. 2. A change in the timing of measurement of SRL and CsA trough whole-blood concentrations was made, detailed contents for AE assessment and management were added.
17 December 2007	Immune inhibition is tend to be more stabilized at 6 months after transplantation than an early stage of transplantation, therefore, SRL trough level should be maintained 15-30 ng/ml at 6months and 12-24 ng/ml at 7-12 months after transplantation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported