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

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

85 years and over	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)

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 (≥) 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)

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 (≥) 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 ± 12.69	 -	
Gender categorical Units: Subjects			
Female	47	47	
Male	32	32	

End points

End points reporting groups

Reporting group title	Sirolimus (SRL)

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 (≥) 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]

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

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)

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

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 (± 15.25)			
12 months	71.92 (± 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 (± 3.64)			
6 months	1.3 (± 0.36)			
12 months	1.25 (± 0.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subject and Graft Survival

End point title	Subject and Graft Survival

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

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

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

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Sirolimus (SRL)

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

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

Blood cholesterol increased				
subjects affected / exposed	29 / 79 (36.71%)			
occurrences (all)	31			
Alanine aminotransferase increased				
subjects affected / exposed	17 / 79 (21.52%)			
occurrences (all)	18			
Aspartate aminotransferase increased				
subjects affected / exposed	12 / 79 (15.19%)			
occurrences (all)	15			
Urine output decreased				
subjects affected / exposed	11 / 79 (13.92%)			
occurrences (all)	12			
Blood lactate dehydrogenase increased				
subjects affected / exposed	10 / 79 (12.66%)			
occurrences (all)	10			
Blood creatinine increased				
subjects affected / exposed	9 / 79 (11.39%)			
occurrences (all)	11			
Hepatic enzyme increased				
subjects affected / exposed	9 / 79 (11.39%)			
occurrences (all)	9			
Blood triglycerides increased				
subjects affected / exposed	8 / 79 (10.13%)			
occurrences (all)	8			
Blood glucose increased				
subjects affected / exposed	8 / 79 (10.13%)			
occurrences (all)	8			
Weight increased				
subjects affected / exposed	5 / 79 (6.33%)			
occurrences (all)	5			
Blood pressure increased				
subjects affected / exposed	4 / 79 (5.06%)			
occurrences (all)	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	19 / 79 (24.05%)		
occurrences (all)	19		
Leukopenia			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Neutropenia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Leukocytosis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Eye disorders			
Visual disturbance			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Xerophthalmia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Conjunctivitis			

subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Conjunctival oedema			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	31 / 79 (39.24%)		
occurrences (all)	36		
Diarrhoea			
subjects affected / exposed	21 / 79 (26.58%)		
occurrences (all)	27		
Nausea			
subjects affected / exposed	16 / 79 (20.25%)		
occurrences (all)	16		
Mouth ulceration			
subjects affected / exposed	14 / 79 (17.72%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	13 / 79 (16.46%)		
occurrences (all)	13		
Abdominal pain			
subjects affected / exposed	12 / 79 (15.19%)		
occurrences (all)	12		
Dyspepsia			
subjects affected / exposed	8 / 79 (10.13%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	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	1 / 79 (1.27%)		
occurrences (all)	1		
Skin disorder			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Dermal cyst			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Blister			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Toxic skin eruption			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Proteinuria			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	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	2 / 79 (2.53%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Coccydynia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Arthritis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	26 / 79 (32.91%)		
occurrences (all)	43		
Nasopharyngitis			
subjects affected / exposed	12 / 79 (15.19%)		
occurrences (all)	18		
Urinary tract infection			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	7		
Herpes zoster			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	6		
Herpes simplex			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	5		
Rhinitis			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	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	1 / 79 (1.27%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Orchitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	19 / 79 (24.05%)		
occurrences (all)	19		
Hyperlipidaemia			
subjects affected / exposed	12 / 79 (15.19%)		
occurrences (all)	12		
Hyperkalaemia			
subjects affected / exposed	8 / 79 (10.13%)		
occurrences (all)	8		
Hypokalaemia			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	7		
Hypoalbuminaemia			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Diabetes mellitus			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	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