PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Rapamune® / Sirolimus

PROTOCOL NO.: 0468H1-101497 (B1741166)

PROTOCOL TITLE: A Randomized Open-Label Study to Compare the Safety and Efficacy of Two Different Sirolimus Regimens With a Tacrolimus + Mycophenolate Mofetil Regimen in De Novo Renal Allograft Recipients

Study Centers: Fifty-six (56) centers took part in the study and randomized subjects; 31 in the United States; 4 each in Germany, Canada and Australia; 3 each in Italy and Spain; 2 each in Belgium and Poland; 1 each in France, Switzerland and the United Kingdom.

Study Initiation and Final Completion Dates: 25 March 2004 to 31 January 2008

Phase of Development: Phase 4

Study Objectives:

- To demonstrate the superiority of sirolimus (SRL) + tacrolimus (TAC) elimination + corticosteroids (Group 1) and SRL + mycophenolate mofetil (MMF) + corticosteroids (Group 2) to TAC + MMF + corticosteroids (Group 3) with respect to renal allograft function at Month 12 post-transplantation;

- To evaluate the safety of all 3 regimens.

METHODS

Study Design: This was a randomized, open-label, comparative, multicenter, Phase 4 study conducted in de novo renal allograft recipients. A total of 420 subjects were planned for randomization in an approximate 1:1:1 ratio to 1 of the 3 treatment groups listed below:

- Group 1 (SRL + TAC elimination + corticosteroids);

- Group 2 (SRL + inosine monophosphate dehydrogenase (IMPDH) inhibitor + corticosteroids);

- Group 3 (TAC + IMPDH inhibitor + corticosteroids).

Random assignment was performed before transplantation and subjects were stratified by race, Black versus Nonblack. Study treatment was initiated within 48 hours after transplantation and was continued for up to 104 weeks, until study end. All randomly assigned subjects who also underwent transplantation were to be followed up for 104 weeks,

regardless of whether the subject remained on the study regimen. The treatments administered to the 3 groups were as follows:

- Subjects in Group 1 received SRL 5 mg/day orally after a loading dose of up to 15 mg within 48 hours after transplantation; TAC was initiated within 24 hours before or after transplantation as an oral dose of up to 0.2 mg/kg/day (in divided doses). The dose of TAC was reduced by 25% per week beginning at the Week 13 visit.

- Subjects in Group 2 received SRL as described above; IMPDH inhibitor was initiated within 24 hours before or after transplantation as an oral dose of up to 2 g/day (in divided doses).

- Subjects in Group 3 received TAC and IMPDH inhibitor as described above.

Doses of SRL and TAC were adjusted to maintain target trough concentrations. Corticosteroids and daclizumab were also administered to all treatment groups. Subjects were to be followed for 24 months whether or not they continued the assigned therapy. Most subjects in Group 2 were discontinued early from the study due to sponsor-termination of this treatment group. Therefore, 24-month follow-up was limited for this group.

The study flowchart is summarized in Table 1 and Table 2. If a subject could not remain on their assigned therapy, then they were considered Off-therapy and followed according to study Table 2. Off-therapy subjects were defined as subjects who discontinued their participation, discontinued their assigned treatment regimen, were withdrawn from the study before the end of the 24 month (104 week) treatment period, who did not initiate assigned treatment by Day 14 post-transplant, or had their immunosuppressive therapy withheld for more than 7 days.

Table 1. Study Flowchart for On-Therapy Subjects

Days (Approximate)	**Screening/ Pre-Transplant Baseline**[a]	**Day 0 (Day of Transplant)**[b]	**Day 4 or Within 1 Day of Hospital Discharge**	**Days 5-7 After First Dose of SRL & TAC**[c]	**Day of Hospital Discharge or Day 14**				**Day 28 Post-Transplantation**						**End of Treatment Phase**
Approximate Weeks (Months) Post-Transplant						**Week 1**	**Week 2**	**Week 3**	**Week 4 (Month 1)**	**Week 13**	**Week 26 (Month 6)**	**Week 39 (Month 9)**	**Week 52 (Month 12)**	**Week 78 (Month 18)**	**Week 104 (Month 24)**
Informed consent	X														
Adverse event collection[d]	<----------														---------->
Medical history	X														
Physical exam	X[e]		X[f]			X[g]	X[g]	X[g]	X[f]	X[f]	X[e]	X[f]	X[e]	X[e]	X[e]
Vital signs[h]	X		X						X	X	X	X	X	X	X
Chest X-ray (P/A)[i]	X														
Hematology, fasting blood chemistry, & fasting lipid profile[j]	X		X						X	X	X	X	X	X	X
Serum creatinine & BUN or urea			X			X	X	X	X	X	X	X	X	X	X
Spot urine protein & creatinine											X		X	X	X
Serum pregnancy test[k]	X														
CMV antibody (IgG)[l]	X														
Initiation of assigned therapy[m]		X													
Daclizumab induction[n]		X			X										
SRL and TAC trough levels				X					X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]
Subject and graft survival											X		X	X	X

BUN = blood urea nitrogen; CMV = cytomegalovirus; CRF = case report form; IgG = Immunoglobulin G; MMF = mycophenolate mofetil; P/A = posterioanterior; SRL = sirolimus; TAC = tacrolimus.

Table 1. Study Flowchart for On-Therapy Subjects

a. Screening/Baseline evaluations were performed within 1 week before renal transplantation.
b. Day 0 was day of transplantation; Day 1 was the day after transplantation.
c. SRL whole blood trough levels were to be obtained 5 to 7 days after the first dose of sirolimus. TAC trough levels were to be obtained 5 to 7 days after the first dose of TAC.
d. Adverse event collection began immediately following obtained informed consent. Adverse events and serious adverse events were collected through Month 25.
e. A complete physical examination including weight were done at Screening/Baseline and at Weeks 26, 52, 78, and 104. Height was obtained at screening only.
f. A limited physical exam included: heart, lungs, abdominal, and neurological exams as well as weight measurement at Day 4 or within 1 day of hospital discharge, and at Weeks 4, 13, and 39.
g. Weight only.
h. Vital signs included blood pressure, pulse, and temperature.
i. Chest x-rays were performed at Screening unless obtained within 3 months before study entry; results were recorded on the CRF, but verification that the subject met the exclusion criterion was made.
j. Safety laboratory determinations.
k. A qualitative serum pregnancy test was done on females of childbearing potential at screening. Results were recorded on the CRF, but verification that the subject met the inclusion criterion was made.
l. For CMV negative recipient only.
m. SRL therapy began within 48 hours post-transplantation; TAC, MMF, and corticosteroid therapy began within 24 hours before or after transplantation.
n. Daclizumab induction (2 mg/kg, maximum of 100 mg) was administered on the day of transplant and up to 2 mg/kg, (maximum of 100 mg) on day of hospital discharge or Day 14.
o. SRL and TAC whole-blood trough levels were obtained at Weeks 4, 13, 26, 39, 52, 78, and 104; and during suspected acute rejection episodes. Trough levels were obtained weekly during TAC taper and at the discretion of the Investigator.

Table 2. Study Flowchart for Off-Therapy Subjects

Approximate Weeks (Months) Post-Transplant	Week 26 (Month 6)	Week 52 (Month 12)	Week 78 (Month 18)	Week 104 (Month 24)
Weight	X	X	X	X
Serum creatinine and BUN or urea	X	X	X	X
Subject and graft survival[a]	X	X	X	X
Adverse event collection[b]				

BUN = blood urea nitrogen.

a. For those subjects who experienced a graft loss, only subject survival was collected after the graft loss at the above mentioned time points. No other evaluations were performed

b. Adverse event collection began immediately following obtaining informed consent. For subjects who discontinued their assigned therapy prior to 24 months, all adverse events were collected for 30 days beyond discontinuation of assigned therapy. Thereafter, only selected adverse events were collected.

Number of Subjects (Planned and Analyzed): The number of subjects planned for this study was 420 (140 subjects per group). The actual number of subjects randomly assigned to the study was 469. Nineteen (19) of these subjects did not undergo transplantation, and an additional 7 subjects did not receive at least 1 dose of the assigned therapy. Therefore, the total number of subjects included in the study analysis is 443 modified intent-to-treat (mITT), including 152 subjects each in Groups 1 and 2 and 139 subjects in Group 3.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria: Male and female subjects aged ≥18 years, who had end-stage renal disease that were scheduled to receive a primary or secondary renal allograft from a deceased, a living-unrelated or a living-related donor. Women of childbearing potential must have had a negative serum pregnancy test before randomization and agreed to use a medically acceptable method of contraception throughout the treatment period and for 3 months following discontinuation of assigned treatment.

Main Exclusion Criteria: Subjects with, evidence of active systemic or localized major infection; known hypersensitivity to SRL or its derivatives, macrolide antibiotics, corticosteroids, daclizumab, TAC or MMF; multiple organ transplants (ie, prior or concurrent transplantation of any organs other than renal transplant); body mass index >32 kg/m^2; recipients of adult or pediatric en block kidney transplants or of nonheart beating donor kidney transplants and African American subjects receiving a second kidney transplant, were excluded from enrollment.

Study Treatment: The study drug was administered only to subjects who were eligible and had provided signed informed consent. Once the study drug had been assigned to a subject, it was not to be reassigned to another subject. Randomly assigned treatments were as follows:

Group 1: SRL + TAC Elimination + Corticosteroids: SRL was initiated within 48 hours after transplantation with an oral loading dose of up to 15 mg, followed by 5 mg/day, to be dose adjusted to maintain a trough concentration of 8 to 15 ng/mL through Week 13. Following

TAC elimination, the target SRL trough concentration was to be 12 to 20 ng/mL to the end of the 2-year treatment phase (Week 104).

Corticosteroids were administered according to local standard of care and were tapered to a minimum of 5 mg/day of prednisone orally (or equivalent every other day) by the end of Week 13. Withdrawal of corticosteroids was prohibited.

TAC was initiated within 24 hours before or after transplantation with an oral dose of up to 0.2 mg/kg/day (in divided doses twice daily [BID]), to be dose adjusted to maintain a target trough concentration of 6 to 15 ng/mL through Week 13. Beginning at the Week 13 visit, TAC dose administration was progressively decreased by 25% per week until fully eliminated.

TAC was not to be eliminated in subjects meeting any of the following criteria:

- Banff Grade 3 acute rejection or vascular rejection in the 4 weeks prior to TAC elimination.
- Dialysis dependency.
- Serum creatinine >4.5 mg/dL.
- Inadequate renal function to support TAC elimination (in the opinion of the Investigator).
- SRL trough concentration <8 ng/mL.

Starting at the Week 13 visit, subjects had up to 4 weeks to complete elimination of TAC. If elimination could not begin at the Week 13 visit, subjects could begin within 6 weeks after the Week 13 visit, and had up to 4 weeks to complete elimination of TAC. Subjects who did not complete elimination by Week 23 entered the off-therapy phase.

Following elimination of TAC, subjects were permitted to resume TAC administration for up to 14 days (1 acute rejection episode) at the Investigator's discretion. If such subjects required resumption of TAC on >1 occasion, or if TAC was required for >14 days, these subjects entered the off-therapy phase.

Group 2: SRL + IMPDH Inhibitor + Corticosteroids: SRL was initiated within 48 hours after transplantation with an oral loading dose of up to 15 mg, followed by 5 mg/day to be dose adjusted to maintain a SRL trough concentration of 10 to 15 ng/mL through Week 13, 8 to 15 ng/mL through Week 26, and 5 to 15 ng/mL through the end of the 2-year treatment period (Week 104). With implementation of protocol amendment 2, the target trough levels were changed to 10 to 15 ng/mL through Week 26, and 8 to 15 ng/mL through the end of the 2-year treatment phase (Week 104).

Corticosteroids were administered according to local standard of care and were tapered to a minimum of 5 mg/day of prednisone orally (or equivalent every other day) by the end of Week 13. Withdrawal of corticosteroids was prohibited.

Mycophenolate was initiated within 24 hours before or after transplantation with an oral dose of up to 2 g/day. Following initiation of mycophenolate, 2 g/day of MMF or 1440 mg/day of

mycophenolate sodium (MPS [in divided doses, BID]) was continued through the end of the 2-year treatment phase (Week 104). Dose reduction was permitted for intolerance; however, a minimum of 1 g/day MMF or 720 mg/day MPS was required.

In June 2006, all subjects in Group 2 who had not already completed Week 104 (on therapy or off-therapy) discontinued from the assigned study therapy and were defined as "Sponsor-terminated." This termination was in response to a higher than expected rate of acute rejection and a numerical difference in number of deaths in Group 2 of this study and in subjects who were administered a similar regimen in the study (A Randomized, Open-Label, Comparative Evaluation of the Safety and Efficacy of Sirolimus Versus Cyclosporine When Combined in a Regimen Containing Basiliximab, Mycophenolate Mofetil, and Corticosteroids in Primary De Novo Renal Allograft Recipients [NCT00137345]) . Following Sponsor-termination, subjects were transitioned to alternative immunosuppressive regimens, if appropriate, according to best local practices.

Group 3: TAC + IMPDH Inhibitor + Corticosteroids: TAC was initiated within 24 hours before or after transplantation with an oral dose of up to 0.2 mg/kg/day (in divided doses, BID) and to be dose adjusted to maintain a target trough concentration of 8 to 15 ng/mL through Week 26, and 5 to 15 ng/mL through the end of the 2-year treatment phase (Week 104).

Corticosteroids were administered according to local standard of care and were tapered to a minimum of 5 mg/day of prednisone orally (or equivalent every other day) by the end of Week 13. Withdrawal of corticosteroids was prohibited.

Mycophenolate was initiated within 24 hours before or after transplantation with an oral dose of up to 2 g/day. Following initiation of mycophenolate, 2 g/day MMF or 1440 mg/day MPS (in divided doses, BID) was continued through the end of the 2-year treatment phase (Week 104). Dose reduction was permitted for intolerance; however, a minimum of 1 g/day MMF or 720 mg/day MPS was required.

Other Treatments: Daclizumab, 2 mg/kg (maximum of 100 mg) was administered to all subjects on Day 0 (day of transplantation) and up to 2 mg/kg (maximum of 100 mg) on day of hospital discharge or no later than Day 14. If a subject was treated with thymoglobulin, or any other non-IL-2 receptor antibody for delayed graft function, the second dose of daclizumab could have been withheld.

Efficacy Endpoints:

Primary Endpoint: Calculated creatinine clearance (Nankivell method) at 12 months (52 weeks) after transplantation.

Secondary Endpoints:

- Calculated creatinine clearance (Nankivell method) at 26, 78, and 104 weeks post-transplantation.
- Serum creatinine at 26, 52, 78, and 104 weeks post-transplantation.

- Subject and graft survival at 26, 52, 78, and 104 weeks post-transplantation. Graft loss is defined as physical loss (nephrectomy), functional loss (necessitating maintenance dialysis for >8 consecutive weeks), re-transplant, or death.
- Incidence and severity of biopsy-confirmed acute rejection including antibody-mediated rejection (immediate [hyperacute] and delayed [accelerated acute]) at 26, 52, 78, and 104 weeks post-transplantation.
- Severity of rejection including a histological grade of the first acute rejection episode (Banff criteria, 1997 version).
- Time to first biopsy-confirmed acute rejection.
- Incidence of antibody use in treatment of acute rejection.
- Incidence of adverse events (AEs).
- Use of insulin initiated post-transplantation (>30 consecutive days).
- Incidence of anemia, defined as hemoglobin <10 g/dL.
- Use of erythropoietin therapy.
- Incidence of wound healing complications.
- Change from Baseline of total cholesterol, triglycerides, low density lipoproteins (LDL)-cholesterol, high density lipoproteins (HDL)-cholesterol at 26, 52, 78, and 104 weeks post-transplantation.
- Frequency of subjects using lipid-lowering therapy.
- Frequency of subjects adding or discontinuing antihypertensive medications.
- Incidence of tremor.
- Incidence of malignancy, including post-transplant lymphoproliferative disorder.
- Incidence of delayed graft function.
- Change in serum creatinine (between 26 and 52 weeks, between 26 and 78 weeks, and between 26 and 104 weeks).
- Slope of creatinine clearance (between 26 and 52 weeks, between 26 and 78 weeks, and between 26 and 104 weeks).
- Percent of subjects in Group 1 (SRL + TAC elimination) requiring resumption of TAC therapy.
- Spot urine protein and protein-creatinine ratio at 26, 52, 78, and 104 weeks post-transplantation.

Safety Evaluations: Subjects were monitored throughout the study for occurrence of all AEs. Hematology, blood chemistries including C-reactive protein and fasting lipid profiles [including total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides, blood urea nitrogen or urea, serum creatinine were taken for safety laboratory tests. Physical examination (including weight), vital signs (blood pressure, pulse, temperature) were conducted at Screening, at intervals during the treatment period and at the end of treatment.

Statistical Methods: The efficacy data were summarized for the mITT population. The mITT population was defined as all randomized subjects who had a kidney transplant and had received at least 1 dose of study drug (SRL or TAC for Group 1, SRL for Group 2, and TAC for Group 3).

The primary endpoint was the calculated creatinine clearance at 52 weeks (12 months) using the Nankivell method for the following groups: Group 1 (SRL + TAC elimination) versus Group 3 (TAC + IMPDH inhibitor) and Group 2 (SRL + IMPDH inhibitor) versus Group 3. The analyses were done with a one-way analysis of variance with treatment group as the factor.

Continuous secondary endpoints were analyzed similarly to the calculated creatinine clearance; where appropriate, baseline values were included in the statistical model.

Secondary endpoints, which are binary data, eg, acute rejection rates, were summarized by reporting the 95% confidence interval on the estimates of these rates. Comparisons between treatment groups were made with chi-square tests.

Severity of acute rejection was analyzed with a generalized Cochran-Mantel-Haenszel row mean score test. Time-to-event endpoints were summarized with Kaplan-Meier statistics.

The mITT population was used for the safety analyses. The counts and percentages of the number of subjects having at least 1 treatment-emergent adverse event (TEAE) for each preferred term and body system term were tabulated.

The distribution of the clinical laboratory results was summarized for each relevant time point. The distribution of vital sign measurements at each relevant time was also summarized.

RESULTS

Subject Disposition and Demography: The actual number of subjects randomly assigned to the study was 469. Nineteen (19) of these subjects did not undergo transplantation, and an additional 7 subjects did not receive at least 1 dose of the assigned therapy. Therefore, the total number of subjects included in the study analysis is 443 (mITT), including 152 subjects each in Groups 1 and 2 and 139 subjects in Group 3.

The primary reasons (n, %) for withdrawal from the study are summarized in Table 3. Overall, 226 (51%) subjects discontinued from the study: 48 (32%) subjects in Group 1, 150 (99%) subjects in Group 2, and 28 (20%) subjects in Group 3. Most of the subjects in Group 2 were discontinued from the study due to Sponsor-termination of the treatment group because of a higher than expected rate of acute rejection in this group.

Table 3. Conclusion Summary of Subject Disposition

Conclusion Status Reason[a]	Treatment			
	Group 1 SRL/TAC (n=152)	Group 2 SRL/MMF (n=152)	Group 3 TAC/MMF (n=139)	Total (N=443)
Discontinued	48 (31.58)	150 (98.68)	28 (20.14)	226 (51.02)
Lost to follow up	6 (3.95)	5 (3.29)	7 (5.04)	18 (4.06)
Voluntarily withdrew	6 (3.95)	6 (3.95)	7 (5.04)	19 (4.29)
Deceased	8 (5.26)	8 (5.26)	4 (2.88)	20 (4.51)
Dropped subject	1 (0.66)	0	1 (0.72)	2 (0.45)
Other	27 (17.76)	131 (86.18)	9 (6.47)	167 (37.70)

MMF = mycophenolate mofetil; n = number of subjects in each treatment group; N = total number of subjects; SRL = sirolimus; TAC = tacrolimus.

a. Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.

Overall, 279 (63%) subjects transitioned to off-therapy, including 88 (57.9%) subjects in Group 1, 150 (98.7%) subjects in Group 2, and 41 (29.5%) subjects in Group 3. In any of the 3 groups, AEs were the most common reason for transition to off-therapy (52 [34.2%] subjects in Group 1, 51 [33.6%] subjects in Group 2, and 31 [22.3%] subjects in Group 3). Most of the subjects in Group 2 were transitioned to off-therapy because of the early termination of this treatment arm by the Sponsor.

A summary of the subject (recipient) demography is presented in Table 4. The mITT population consisted of 443 subjects (300 male and 143 female subjects) between 19 and 76 years of age (mean age 49 years). Most of the baseline characteristics were similar across the 3 groups. The mean number of human leukocyte antigen -mismatches, pretransplant cytomegalovirus immunoglobulin G status, mean number of previous transplants, and mean duration of pretransplant dialysis were similar across the 3 groups.

Table 4. Conclusion Demography of Recipient

Characteristic	p-Value	Treatment			Total
		Group 1 SRL/TAC (n=152)	Group 2 SRL/MMF (n=152)	Group 3 TAC/MMF (n=139)	(N=443)
Recipient age	0.223[a]				
Mean		47.91	50.39	48.4	48.92
Standard deviation		13.30	12.89	13.23	13.15
Sex	0.016[b]				
Male		109 (71.71)	110 (72.37)	81 (58.27)	300 (67.72)
Female		43 (28.29)	42 (27.63)	58 (41.73)	143 (32.28)
Ethnic origin	0.954[b]				
Caucasian		114 (75.00)	117 (76.97)	102 (73.38)	333 (75.17)
Black		14 (9.21)	17 (11.18)	15 (10.79)	46 (10.38)
Asian		6 (3.95)	4 (2.63)	5 (3.60)	15 (3.39)
Other		18 (11.84)	14 (9.21)	17 (12.23)	49 (11.06)
Height	0.075[a]				
Mean		171.49	172.05	169.47	171.05
Standard deviation		10.35	10.26	9.55	10.11
Weight	0.038[a]				
Mean		77.87	75.25	73.12	75.48
Standard deviation		16.11	15.84	15.42	15.89
Primary etiology	0.618[b]				
Hypertension		22 (14.47)	22 (14.47)	17 (12.23)	61 (13.77)
Diabetes mellitus - Type I		9 (5.92)	10 (6.58)	7 (5.04)	26 (5.87)
Diabetes mellitus - Type II		18 (11.84)	18 (11.84)	10 (7.19)	46 (10.38)
Polycystic kidney disease		11 (7.24)	17 (11.18)	21 (15.11)	49 (11.06)
Obstructive uropathy		2 (1.32)	4 (2.63)	2 (1.44)	8 (1.81)
Glomerulonephritis		38 (25.00)	33 (21.71)	27 (19.42)	98 (22.12)
Other		52 (34.21)	48 (31.58)	55 (39.57)	155 (34.99)
Number of HLA mismatch	0.944[a]				
Mean		3.38	3.36	3.32	3.35
Standard deviation		1.54	1.69	1.69	1.64
Pre-transplant CMV (IgG) antibody status	0.381[b]				
Negative		65 (42.76)	56 (36.84)	44 (31.65)	165 (37.25)
Positive		84 (55.26)	94 (61.84)	92 (66.19)	270 (60.95)
Unknown		3 (1.97)	2 (1.32)	3 (2.16)	8 (1.81)
Peak panel of reactive antibodies (%PRA)	0.212[a]				
Mean		6.15	13.32	6.65	8.77
Standard deviation		17.25	62.48	18.32	39.38
Number of previous transplants	0.914[a]				
Mean		0.07	0.09	0.08	0.08
Standard deviation		0.26	0.28	0.27	0.27

Discrete variables – Recipients sex, race, primary etiologies, pretransplant CMV(IgG) status, and dialysis(Y/N).
Continuous variables – age, height, weight, systolic and diastolic BP, pulse, %PRA, HLA mismatches, and duration of dialysis.

Table 4. Conclusion Demography of Recipient

BP = blood pressure; CMV = cytomegalovirus; HLA = human leukocyte antigen ; IgG = immunoglobulin G; MMF = mycophenolate mofetil; n = number of subjects with pre-specified criteria in each treatment group; N = total number of subjects; PRA = peak panel of reactive antibodies; SRL = sirolimus; TAC = tacrolimus.
a. One-way analysis of variance with treatment as factor.
b. p-value for Chi-square.

A summary of the demography of the donors is presented in Table 5. The demographic characteristics of the renal allograft donors were similar across the groups. The mean age of the donors across the groups ranged from 43.23 to 45.54 years (overall mean age 44.38 years). Most of the donors were of Caucasian origin. The donor organ ischemia time was similar in all the groups (approximately 12 hours).

Table 5. Demography of Donor

Characteristic	p-Value	Treatment			
		Group 1 SRL/TAC (n=152)	Group 2 SRL/MMF (n=152)	Group 3 TAC/MMF (n=139)	Total (N=443)
Donor age	0.365[a]				
Mean		43.23	45.54	44.39	44.38
Standard deviation		13.63	14.93	13.85	14.16
Missing		0	0	0	0
Donor ethnic origin	0.982[b]				
Caucasian		115 (75.66)	116 (76.32)	100 (71.94)	331 (74.72)
Black		9 (5.92)	8 (5.26)	9 (6.47)	26 (5.87)
Asian		1 (0.66)	2 (1.32)	2 (1.44)	5 (1.13)
Other		27 (17.76)	25 (16.45)	27 (19.42)	79 (17.83)
Missing		0	1	1	2
Donor organ ischemia time (total hours)	0.999[a]				
Mean		12.06	12.04	12	12.03
Standard deviation		9.71	9.10	9.14	9.31
Missing		0	1	2	3
Donor organ ischemia time (cold hours)	0.980[a]				
Mean		11.54	11.53	11.73	11.6
Standard deviation		9.59	8.90	9.12	9.19
Missing		0	4	1	5
Donor organ source	0.795[b]				
Cadaveric		92 (60.53)	96 (63.16)	89 (64.03)	277 (62.53)
Living related		36 (23.68)	39 (25.66)	31 (22.30)	106 (23.93)
Living unrelated		24 (15.79)	17 (11.18)	19 (13.67)	60 (13.54)
Donor CMV IgG status	0.721[b]				
Negative		55 (36.18)	60 (39.47)	49 (35.25)	164 (37.02)
Positive		90 (59.21)	86 (56.58)	87 (62.59)	263 (59.37)
Unknown		7 (4.61)	6 (3.95)	3 (2.16)	16 (3.61)
Donor gender	0.212[b]				
Male		80 (52.63)	92 (60.53)	71 (51.08)	243 (54.85)
Female		72 (47.37)	60 (39.47)	68 (48.92)	200 (45.15)

Discrete variables - donor ethnicity source and CMV IgG.
Continuous variables - donor age and ischemia time.
CMV = cytomegalovirus; IgG = immunoglobulin G; MMF = mycophenolate mofetil; n = number of subjects with pre-specified criteria in each treatment group; N = total number of subjects; SRL = sirolimus; TAC = tacrolimus.

a. One-way analysis of variance with treatment as factor.
b. Fisher's exact test p-value (2-tail).

Efficacy Results:

Because of early termination of the treatment in Group 2, the duration of the study drug exposure in this group was less than in Groups 1 and 3. Therefore, comparing the data between Group 2 and the other 2 groups must be taken into account as it may be misleading.

Primary Efficacy Endpoints:

Calculated Creatinine Clearance (Nankivell Method) at 12 Months (Week 52) After Transplantation:

At Week 52, the mean calculated creatinine clearance was 59 mL/min in Groups 1 and 2, and 62 mL/min in Group 3. There were no significant differences in the mean calculated creatinine clearance between Group 1 and Group 3 (p=0.285) and between Group 2 and Group 3 (p=0.328) (Table 6).

Table 6. Summary of Nankivell Calculated Creatinine Clearance at Week 52 by Treatment Group (Modified Intent-to-Treat Population)

Time	Therapy	Number of Subjects	Mean (Std Dev)	Median	Min-Max	p-Value (t-test wrt Group 3)
Week 52	SRL/TAC (Group 1)	151	59.06(23.85)	63.22	0.00-99.59	0.285
	SRL/MMF (Group 2)	152	59.28(24.26)	62.60	0.00-115.02	0.328
	TAC/MMF (Group 3)	138	61.96(22.06)	64.71	0.00-108.79	

Glomerular filtration rate (GFR) was assigned 0 for negative GFR, graft loss or death; last observation carried forward for missing values.
min-max = minimum-maximum; MMF = mycophenolate mofetil; SRL = sirolimus; Std Dev = standard deviation; TAC = tacrolimus; wrt = with respect to.

Secondary Efficacy Endpoints:

Calculated Creatinine Clearance (Nankivell Method) at 26, 78, and 104 Weeks Posttransplantation:

The summary statistics for the calculated creatinine clearance for the mITT population is presented in Table 7. The renal function was similar when Group 1 was compared with Group 3 at 26, 52, 78, and 104 weeks after transplantation and Group 2 compared with Group 3 at 26 and 52 weeks after transplantation.

Of note, there were not enough subjects in Group 2 at 78 and 104 weeks after transplantation because of Sponsor-termination of this treatment arm, and therefore, no comparison was made with Group 3 at these time points.

Table 7. Summary of Nankivell Calculated Creatinine Clearance (Modified Intent-to-Treat Population)

Time	Therapy	Number of Subjects	Mean (Std Dev)	Median	Min-Max	p-Value (t-test wrt Group 3)
Day 4	SRL/TAC (Group 1)	143	45.98(27.11)	44.46	0.00-135.87	0.155
	SRL/MMF (Group 2)	148	43.85(27.39)	45.03	0.00-119.62	0.453
	TAC/MMF (Group 3)	136	41.50(25.34)	40.79	0.00-108.58	
Week 26	SRL/TAC (Group 1)	150	58.28(22.51)	62.06	0.00-101.21	0.098
	SRL/MMF (Group 2)	152	61.00(23.65)	64.02	0.00-154.92	0.583
	TAC/MMF (Group 3)	138	62.39(19.10)	64.64	0.00-107.62	
Week 52	SRL/TAC (Group 1)	151	59.06(23.85)	63.22	0.00-99.59	0.285
	SRL/MMF (Group 2)	152	59.28(24.26)	62.60	0.00-115.02	0.328
	TAC/MMF (Group 3)	138	61.96(22.06)	64.71	0.00-108.79	
Week 78	SRL/TAC (Group 1)	151	59.50(24.50)	62.60	0.00-106.63	0.373
	TAC/MMF (Group 3)	138	61.96(21.94)	65.48	0.00-122.12	
Week 104	SRL/TAC (Group 1)	151	58.26(26.82)	63.51	0.00-119.43	0.183
	TAC/MMF (Group 3)	138	62.19(22.82)	65.97	0.00-120.48	

Glomerular filtration rate (GFR) was assigned 0 for negative GFR, graft loss or death; last observation carried forward for missing values.
min-max = minimum-maximum; MMF = mycophenolate mofetil; SRL = sirolimus; Std Dev = standard deviation; TAC = tacrolimus; wrt = with respect to.

Serum Creatinine at 26, 52, 78, and 104 Weeks Posttransplantation:

In all the 3 groups, the mean serum creatinine at 26, 52, 78, and 104 weeks after transplantation ranged from 120 to 160 μmol/L. At any given time point, the mean serum creatinine was similar when Groups 1 and 2 were each compared with Group 3 (Table 8). Of note, at 104 weeks after transplantation, there were only 10 subjects in Group 2 because of Sponsor-termination of this treatment arm.

Table 8. Summary of Serum Creatinine (µmol/L) by Treatment Group (All Available Data in Modified Intent-to-Treat Population)

Period	Group	Number of Subjects	Mean (Std Dev)	Median	Min-Max	p-Value wrt Group 3[a]
Day 4	SRL/TAC (Group 1)	144	306.07 (246.97)	213.49	53.04-1105.0	0.367
	SRL/MMF (Group 2)	149	330.09 (273.05)	212.16	70.72-1262.4	0.872
	TAC/MMF (Group 3)	136	335.26 (289.67)	191.50	70.72-1343.7	
Week 26	SRL/TAC (Group 1)	136	153.98 (66.21)	141.44	79.56-528.00	0.293
	SRL/MMF (Group 2)	138	142.71 (52.99)	132.60	53.04-450.84	0.780
	TAC/MMF (Group 3)	126	145.07 (83.95)	123.76	70.72-742.56	
Week 52	SRL/TAC (Group 1)	132	157.78 (97.86)	132.60	79.56-942.00	0.240
	SRL/MMF (Group 2)	134	146.59 (76.77)	132.60	61.88-866.32	0.832
	TAC/MMF (Group 3)	121	144.14 (100.63)	123.76	61.88-1060.8	
Week 78	SRL/TAC (Group 1)	122	159.50 (142.88)	131.30	70.72-1530.0	0.102
	SRL/MMF (Group 2)	87	139.90 (53.30)	123.76	61.88-427.00	0.891
	TAC/MMF (Group 3)	116	137.93 (72.08)	119.50	53.04-565.76	
Week 104	SRL/TAC (Group 1)	121	148.46 (71.92)	123.76	70.72-569.00	0.574
	SRL/MMF (Group 2)	10	119.76 (38.80)	106.46	79.56-212.16	0.433
	TAC/MMF (Group 3)	112	142.09 (101.84)	121.38	61.88-1025.4	

ANOVA = analysis of variance; min-max = minimum-maximum; MMF = mycophenolate mofetil; SRL = sirolimus; Std Dev = standard deviation; TAC = tacrolimus; wrt = with respect to.

a. ANOVA model.

Subject and Graft Survival at 26, 52, and 104 Weeks Post Transplantation:

At the time points indicated in Table 9, the rate of graft loss in Group 1 (for the mITT population) was greater than in Group 3. A statistically significant difference between the 2 groups was reached at 6 months and at 2 years. By 2 years of treatment, 10 subjects in Group 1 and 2 subjects in Group 3 had graft losses. By 2 years, 8 subjects in Group 2 had graft losses.

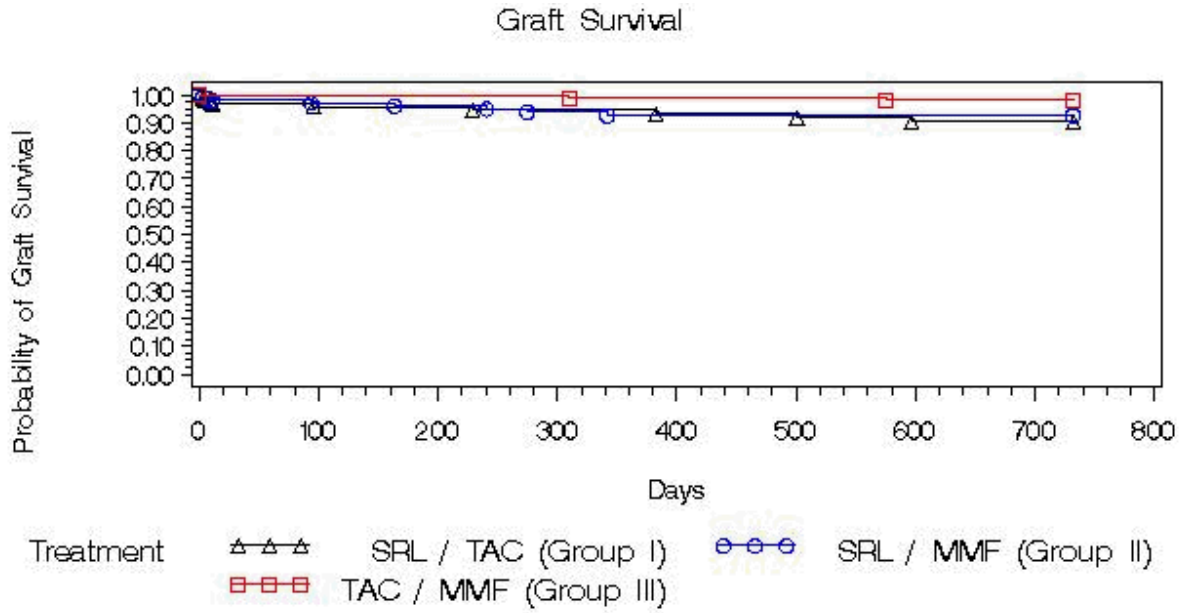
Table 9. Graft Function Loss Rates (Not Including Death) (Modified Intent-to-Treat Population)

Time	Treatment Group	Graft Loss Rates	Risk Diff vs Group 3 (95% CI)	p-Value (Fisher's Test) vs Group 3
Up to 6 months	SRL/TAC (Group 1)	6/152 (3.9%)	3.9% (0.9%, 7.0%)	0.031
	SRL/MMF (Group 2)	5/152 (3.3%)	3.3% (0.5%, 6.1%)	0.062
	TAC/MMF (Group 3)	0/139 (0.0%)		
Up to 1 year	SRL/TAC (Group 1)	7/152 (4.6%)	3.9% (0.3%, 7.5%)	0.069
	SRL/MMF (Group 2)	8/152 (5.3%)	4.5% (0.7%, 8.4%)	0.038
	TAC/MMF (Group 3)	1/139 (0.7%)		
Up to 2 years	SRL/TAC (Group 1)	10/152 (6.6%)	5.1% (0.7%, 9.6%)	0.037
	SRL/MMF (Group 2)	8/152 (5.3%)	3.8% (-0.2%, 7.9%)	0.107
	TAC/MMF (Group 3)	2/139 (1.4%)		

CI = confidence interval;Diff = difference; MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus; vs = versus.

The time to probability of graft survival is shown in Figure 1. The probability of graft survival over time was significantly decreased in Groups 1 (p=0.0098) and 2 (p=0.0221) compared with Group 3.

Figure 1. Graft Survival (Not Including Death) (Modified Intent-to-Treat Population)



MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus.

At any time points shown in Table 10, the subject death rate in Group 1 (for the mITT population) was greater than in Group 3. By 2 years, 8 subjects died in Group 1 compared with 4 subjects in Group 3. In Group 2, by 2 years, there were 8 deaths. Of note, 1 death in Group 3 occurred during the 1-month follow-up period after the last dose of study therapy. This subject was not included in the 2-year analysis.

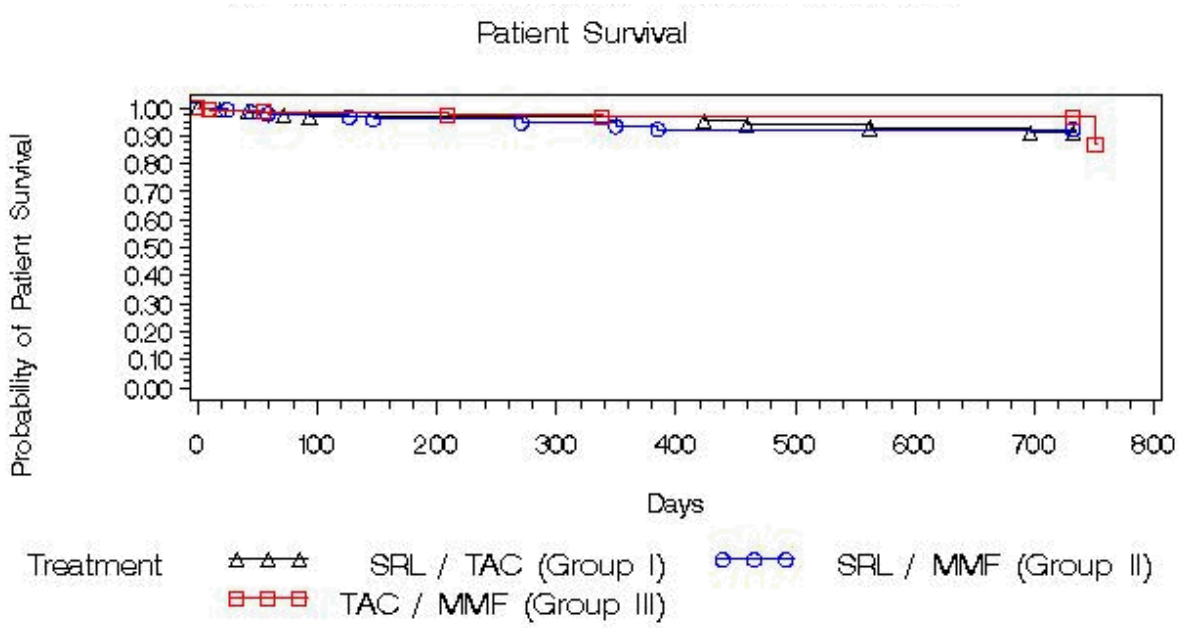
Table 10. Subject Death Rates (Modified Intent-to-Treat Population)

Time	Treatment Group	Death Rates	Risk Diff (95% CI)	p-Value (Fisher's Test)
Up to 6 months	SRL/TAC (Group 1)	4/152 (2.6%)	1.2% (-2.0%, 4.4%)	0.686
	SRL/MMF (Group 2)	5/152 (3.3%)	1.9% (-1.6%, 5.3%)	0.451
	TAC/MMF (Group 3)	2/139 (1.4%)		
Up to 1 year	SRL/TAC (Group 1)	4/152 (2.6%)	-0.2% (-4.0%, 3.5%)	1.000
	SRL/MMF (Group 2)	7/152 (4.6%)	1.7% (-2.6%, 6.1%)	0.546
	TAC/MMF (Group 3)	4/139 (2.9%)		
Up to 2 years	SRL/TAC (Group 1)	8/152 (5.3%)	2.4% (-2.1%, 6.9%)	0.384
	SRL/MMF (Group 2)	8/152 (5.3%)	2.4% (-2.1%, 6.9%)	0.384
	TAC/MMF (Group 3)	4/139 (2.9%)		

CI = confidence interval; Diff = difference; MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus.

The time to probability of subject survival for the 3 groups is shown in Figure 2. There were no significant differences in subject survival between Group 1 and Group 3 (p=0.2352) and between Group 2 and Group 3 (p=0.1746).

Figure 2. Subject Survival (Modified Intent-to-Treat Population)



MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus.

Incidence and Severity of Biopsy-Confirmed Acute Rejection at 6 Months, 1 Year, and 2 Years Posttransplantation:

At the time points presented in Table 11, the rate of acute rejection was not significantly different between Groups 1 and 3. By 2 years, the rates of acute rejection were 16.4% (25/152) in Group 1 and 11.5% (16/139) in Group 3. By 2 years, the rate of acute rejection in Group 2 was 30.9% (47/152).

Table 11. Biopsy-Confirmed Acute Rejection Rates (Modified Intent-to-Treat Population)

Time	Treatment Group	Acute Rejection Rates	Risk Diff (95% CI)	p-Value (Fisher's Test)
Up to 6 months	SRL/TAC (Group 1)	13/152 (8.6%)	2.1% (-4.0%, 8.1%)	0.658
	SRL/MMF (Group 2)	39/152 (25.7%)	19.2% (11.1%, 27.2%)	<.001
	TAC/MMF (Group 3)	9/139 (6.5%)		
Up to 1 year	SRL/TAC (Group 1)	22/152 (14.5%)	6.6% (-0.6%, 13.7%)	0.096
	SRL/MMF (Group 2)	45/152 (29.6%)	21.7% (13.2%, 30.2%)	<.001
	TAC/MMF (Group 3)	11/139 (7.9%)		
Up to 2 years	SRL/TAC (Group 1)	25/152 (16.4%)	4.9% (-3.0%, 12.9%)	0.242
	SRL/MMF (Group 2)	47/152 (30.9%)	19.4% (10.3%, 28.5%)	<.001
	TAC/MMF (Group 3)	16/139 (11.5%)		

CI = confidence interval; Diff = difference; MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus.

Severity of Rejection by a Histological Grade of the First Acute Rejection Episode:

The severity of biopsy-confirmed acute rejection is presented in Table 12. Most of the acute rejection episodes in each group were mild.

Table 12. Severity Distribution of Biopsy-Confirmed Acute Rejection (Modified Intent-to-Treat Population)

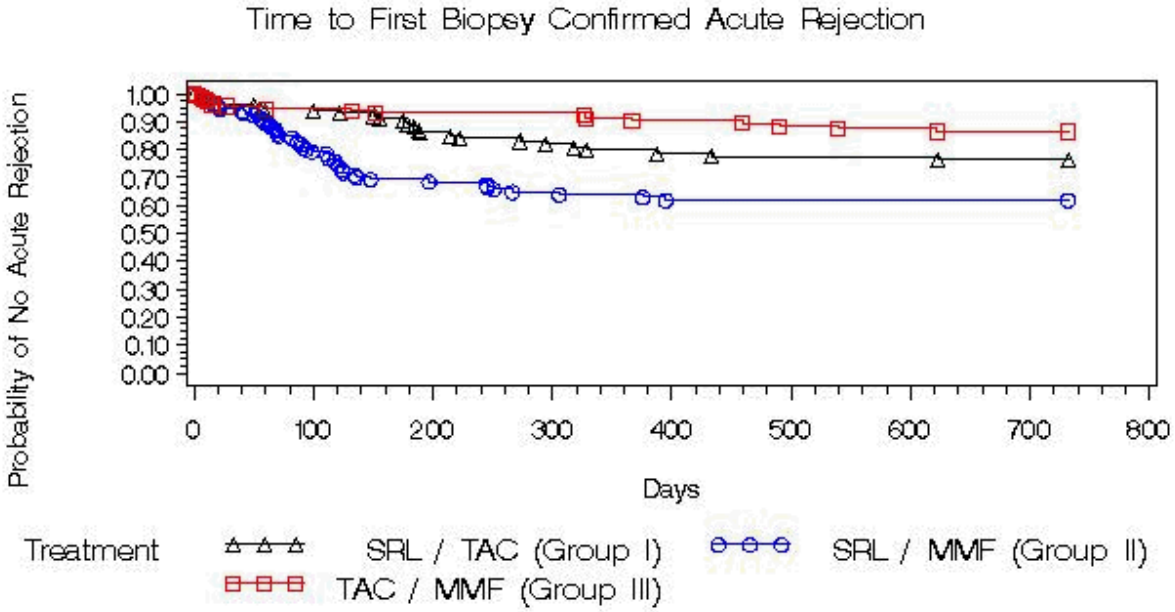
Time	Treatment Group	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	p-Value (CMH Row Mean Score Test)
Up to 6 month	SRL/TAC (Group 1)	76.9% (10/13)	23.1% (3/13)		0.046
	SRL/MMF (Group 2)	71.8%(28/39)	28.2%(11/39)		0.031
	TAC/MMF (Group 3)	33.3% (3/9)	66.7% (6/9)		
Up to 1 year	SRL/TAC (Group 1)	77.3% (17/22)	22.7% (5/22)		0.072
	SRL/MMF (Group 2)	71.1%(32/45)	28.9%(13/45)		0.110
	TAC/MMF (Group 3)	45.5% (5/11)	54.5% (6/11)		
Up to 2 years	SRL/TAC (Group 1)	80.0% (20/25)	20.0% (5/25)		0.223
	SRL/MMF (Group 2)	72.3%(34/47)	27.7%(13/47)		0.462
	TAC/MMF (Group 3)	62.5% (10/16)	37.5% (6/16)		

CMH = Cochrane-Mantel-Haenszel; MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus.

Time to First Biopsy-Confirmed Acute Rejection

The time to first biopsy-confirmed acute rejection is displayed in Figure 3. The log-rank statistics showed no significant difference for this variable in Group 1 versus Group 3 (p=0.0544), but was significant between Group 2 and Group 3 (p <0.0001).

Figure 3. Time to First Biopsy-Confirmed Acute Rejection (Modified Intent-to-Treat Population)



MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus.

Incidence of Anemia:

Sixty-two (62, 40.8%) subjects in Group 1 and 50 (36.0%) subjects in Group 3 had treatment-emergent anemia during the study. There was no significant difference in the incidence of treatment-emergent anemia between the 2 groups (p=0.469). In Group 2, 73 (48.0%) subjects had treatment-emergent anemia during the study.

Use of Erythropoietin Therapy:

Before study initiation, 23 (15.1%) subjects in Group 1 and 21 (15.1%) subjects in Group 3 received erythropoietin therapy. During the study, the number of subjects receiving erythropoietin therapy was 64 (42.1%) in Group 1 and 48 (34.5%) in Group 3. In Group 2, the number of subjects receiving erythropoietin therapy was 19 (12.5%) before the study and 72 (47.4%) during the study.

Incidence of Wound Healing Complications:

There was a significantly greater number of subjects in Group 1 (25, 16.4%) who had treatment-emergent delayed wound healing than those in Group 3 (8, 5.8%) (p=0.005). In Group 2, 35 (23.0%) subjects had treatment-emergent delayed wound healing.

Frequency of Subjects Using Lipid-Lowering Therapy:

Before study initiation, 31 (20.4%) subjects in Group 1 and 21 (15.1%) subjects in Group 3 received lipid lowering agents. During the study, the number of subjects on lipid lowering agents was 105 (69.1%) and 74 (53.2%), respectively. The majority of the subjects within the 2 groups were on 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) inhibitors.

In Group 2, 33 (21.7%) subjects received lipid lowering agents before the study compared with 102 (67.1%) subjects during the study.

Incidence of Tremor:

Treatment-emergent tremor was reported by 33 (21.7%) subjects in Group 1 and 34 (24.5%) subjects in Group 3. There was no significant difference in the incidence of treatment-emergent tremor between the 2 groups (p=0.581). In Group 2, 12 (7.9%) subjects reported treatment-emergent tremor.

Incidence of Malignancy:

Seven (7, 4.6%) subjects in Group 1 and 5 (3.6%) in Group 3 had treatment-emergent malignancy. No significant differences were observed in the reporting rate of malignancy between the 2 groups (p=0.772). The most common malignancy was skin carcinoma in Group 1 (5, 3.3%) and carcinoma (body as a whole) (2, 1.4%)in Group 3. In Group 2, 5 (3.3%) subjects had treatment-emergent malignancy, the most common being skin carcinoma.

Incidence of Delayed Graft Function:

The incidence of delayed graft function was similar when Groups 1 and 2 were each compared with Group 3: 40 (26.3%) subjects in Group 1, 41 (27%) subjects in Group 2, and 38 (27.3%) subjects in Group 3 (Table 13).

Table 13. Delayed Graft Function - (Kidney Failure or Kidney Tubular Necrosis Occurring Within 7 Days of Transplant) (Modified Intent-to-Treat Population)

Treatment Group	DGF Rates	Risk Diff (95% CI)	p-Value wrt Group 3 (Fisher's Test)
SRL/TAC (Group 1)	40/152 (26.3%)	-1.0% (-11.2%, 9.2%)	0.895
SRL/MMF (Group 2)	41/152 (27.0%)	-0.4% (-10.6%, 9.9%)	1.000
TAC/MMF (Group 3)	38/139 (27.3%)		

CI = confidence interval; DGF = delayed graft function; Diff = difference; MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus; wrt = with respect to.

Spot Urine Protein to Creatinine Ratio at 13, 26, 52, 78, and 104 Weeks Posttransplantation:

At Weeks 13, 26, 52, 78, and 104, the median urine protein to creatinine ratio ranged from 0.20 to 0.28 in Group 1, 0.14 to 0.32 in Group 2, and 0.13 to 0.16 in Group 3 (Table 14). Compared with Group 3, the median urine protein to creatinine ratio reached statistical significance in Group 1 at Weeks 26, 52, 78, and 104 and in Group 2 at Weeks 13, 26, and 52.

Table 14. Summary of Urine Protein/Creatinine Ratio By Treatment Group (Modified Intent-to-Treat Population)

Time	Therapy	N	Mean	Median	Range	p-Value (Wilcoxon Test wrt Group 3)	p-Value (Kruskal-Wallis Across 3 Groups)
Week 13	SRL/TAC (Group 1)	39	0.83 (0.45)	0.21	0.06-17.43	0.358	
	SRL/MMF (Group 2)	36	0.43 (0.09)	0.28	0.02-3.05	0.038	
	TAC/MMF (Group 3)	37	0.36 (0.10)	0.16	0.01-3.51		0.117
Week 26	SRL/TAC (Group 1)	60	0.41 (0.06)	0.25	0.02-2.62	0.039	
	SRL/MMF (Group 2)	60	0.41 (0.05)	0.32	0.04-2.04	<.001	
	TAC/MMF (Group 3)	67	0.82 (0.41)	0.16	0.02-27.00		0.002
Week 52	SRL/TAC (Group 1)	54	0.36 (0.05)	0.20	0.01-2.46	0.002	
	SRL/MMF (Group 2)	58	0.52 (0.14)	0.26	0.03-7.94	<.001	
	TAC/MMF (Group 3)	74	0.19 (0.02)	0.15	0.00-0.89		<.001
Week 78	SRL/TAC (Group 1)	44	0.46 (0.08)	0.28	0.06-2.60	0.005	
	SRL/MMF (Group 2)	47	0.26 (0.03)	0.20	0.04-1.15	0.109	
	TAC/MMF (Group 3)	58	0.23 (0.03)	0.15	0.00-1.21		0.011
Week 104	SRL/TAC (Group 1)	44	0.32 (0.05)	0.21	0.04-1.78	0.011	
	SRL/MMF (Group 2)	4	0.60 (0.50)	0.14	0.02-2.10	1.000	
	TAC/MMF (Group 3)	59	0.22 (0.03)	0.13	0.00-1.33		0.037

Excluded 0 for the analysis (either the protein or the creatinine).
MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus; wrt = with respect to.

The following analyses were not performed:

- The primary and secondary endpoints by strata.
- Graft function loss/subject survival at 78 weeks.
- Incidence of antibody use in treatment of acute rejection.
- Use of insulin initiated posttransplantation (>30 consecutive days).
- Change in serum creatinine between 26 and 52 weeks, between 26 and 78 weeks, and between 26 and 104 weeks.

Safety Results:

All subjects in the mITT (n=443) took at least 1 dose of the drug and were included in the safety evaluations: 152 subjects in Group 1 (SRL/TAC elimination), 152 subjects in Group 2(SRL/MMF), and 139 subjects in Group 3 (TAC/MMF). Of the 443 subjects, 217 subjects completed the study (104 subjects in Group 1, 2 subjects in Group 2, and 111 subjects in Group 3). Most of the subjects in Group 2 were discontinued by the Sponsor because of a higher than expected rate of acute rejection in this group. Subjects in Group 2, who were prematurely terminated from the study, were to be followed up for any AEs of special interest (acute rejection, serious infection, life-threatening event, malignancy, death, and graft loss) for up to 24 months after transplantation. Only 68 such subjects provided informed consent for this follow-up.

Because of early termination of the subjects in Group 2, the duration of study drug exposure and AE monitoring in this group was less than those in Groups 1 and 3. Therefore, comparing the AEs between Group 2 and the other 2 groups must be taken into context as it may be misleading. Therefore, direct comparisons between Group 2 and 3 have not been made in many instances.

All subjects randomized to 1 of the 3 treatments and who took at least 1 dose of the drug reported AEs. The number and percentage of subjects reporting AEs by treatment group is presented in Table 15.

Table 15. Number (%) of Subjects Reporting Adverse Events by With an Overall Incidence of ≥5%

Body System[a]	Treatment		
Adverse Event	Group 1	Group 2	Group 3
	SRL/TAC	SRL/MMF	TAC/MMF
	n=152	n=152	n=139
Any adverse event	152 (100.0)	152 (100.0)	139 (100.0)
Adverse events associated with miscellaneous. factors	74 (48.7)	69 (45.4)	64 (46.0)
Local reaction to procedure	66 (43.4)	62 (40.8)	60 (43.2)
Surgical procedure	8 (5.3)	2 (1.3)	4 (2.9)
Trauma	7 (4.6)	14 (9.2)	5 (3.6)
Body as a whole	129 (84.9)	126 (82.9)	106 (76.3)
Abdominal pain	32 (21.1)	27 (17.8)	35 (25.2)
Asthenia	34 (22.4)	30 (19.7)	30 (21.6)
Back pain	14 (9.2)	17 (11.2)	21 (15.1)
Cellulitis	8 (5.3)	4 (2.6)	2 (1.4)
Chest pain	11 (7.2)	8 (5.3)	16 (11.5)
Fever	33 (21.7)	37 (24.3)	20 (14.4)
Generalized edema	10 (6.6)	1 (0.7)	3 (2.2)
Headache	24 (15.8)	15 (9.9)	23 (16.5)
Hernia	6 (3.9)	9 (5.9)	7 (5.0)
Infection	31 (20.4)	46 (30.3)	38 (27.3)
Laboratory test abnormal	16 (10.5)	13 (8.6)	8 (5.8)
Overdose	12 (7.9)	5 (3.3)	10 (7.2)
Pain	31 (20.4)	19 (12.5)	29 (20.9)
Sepsis	17 (11.2)	10 (6.6)	10 (7.2)
Transplant rejection	33 (21.7)	56 (36.8)	26 (18.7)
Cardiovascular system	107 (70.4)	96 (63.2)	85 (61.2)
Cardiovascular physical finding	4 (2.6)	9 (5.9)	5 (3.6)
Hypertension	62 (40.8)	54 (35.5)	48 (34.5)
Hypervolemia	12 (7.9)	10 (6.6)	5 (3.6)
Hypotension	24 (15.8)	23 (15.1)	26 (18.7)
Tachycardia	11 (7.2)	10 (6.6)	12 (8.6)
Thrombosis	12 (7.9)	10 (6.6)	2 (1.4)
Digestive system	103 (67.8)	104 (68.4)	98 (70.5)
Abdominal distension	12 (7.9)	16 (10.5)	13 (9.4)
Anorexia	11 (7.2)	12 (7.9)	10 (7.2)
Constipation	31 (20.4)	28 (18.4)	32 (23.0)
Diarrhea	46 (30.3)	63 (41.4)	59 (42.4)
Dyspepsia	12 (7.9)	10 (6.6)	14 (10.1)
Gastroenteritis	5 (3.3)	5 (3.3)	8 (5.8)
Gastroesophageal reflux disease	3 (2.0)	1 (0.7)	8 (5.8)
Gastrointestinal disorder	4 (2.6)	8 (5.3)	7 (5.0)
Liver function tests abnormal	28 (18.4)	17 (11.2)	7 (5.0)
Nausea	39 (25.7)	40 (26.3)	43 (30.9)
Stomatitis	9 (5.9)	18 (11.8)	7 (5.0)
Vomiting	25 (16.4)	29 (19.1)	29 (20.9)
Endocrine system	42 (27.6)	18 (11.8)	35 (25.2)

Table 15. Number (%) of Subjects Reporting Adverse Events by With an Overall Incidence of ≥5%

Body System[a]	Treatment		
Adverse Event	Group 1	Group 2	Group 3
	SRL/TAC	SRL/MMF	TAC/MMF
	n=152	n=152	n=139
Diabetes mellitus	37 (24.3)	17 (11.2)	24 (17.3)
Hemic and lymphatic system	85 (55.9)	92 (60.5)	75 (54.0)
Anemia	62 (40.8)	73 (48.0)	50 (36.0)
Ecchymosis	15 (9.9)	9 (5.9)	8 (5.8)
Leukocytosis	12 (7.9)	8 (5.3)	14 (10.1)
Leukopenia	15 (9.9)	25 (16.4)	22 (15.8)
Thrombocytopenia	20 (13.2)	25 (16.4)	4 (2.9)
Dehydration	16 (10.5)	7 (4.6)	11 (7.9)
Metabolic and nutritional	130 (85.5)	131 (86.2)	112 (80.6)
Dehydration	16 (10.5)	7 (4.6)	11 (7.9)
Creatinine increased	54 (35.5)	44 (28.9)	38 (27.3)
Edema	15 (9.9)	21 (13.8)	17 (12.2)
Hypercholesteremia	21 (13.8)	23 (15.1)	13 (9.4)
Hyperglycemia	38 (25.0)	32 (21.1)	31 (22.3)
Hyperkalemia	36 (23.7)	17 (11.2)	25 (18.0)
Hyperlipemia	56 (36.8)	65 (42.8)	28 (20.1)
Hypocalcemia	17 (11.2)	9 (5.9)	8 (5.8)
Hypokalemia	16 (10.5)	16 (10.5)	10 (7.2)
Hypomagnesemia	20 (13.2)	6 (3.9)	19 (13.7)
Hypophosphatemia	35 (23.0)	37 (24.3)	34 (24.5)
Lactic dehydrogenase increased	8 (5.3)	10 (6.6)	3 (2.2)
Peripheral edema	78 (51.3)	75 (49.3)	51 (36.7)
Weight gain	17 (11.2)	18 (11.8)	27 (19.4)
Weight loss	9 (5.9)	5 (3.3)	8 (5.8)
Musculoskeletal system	43 (28.3)	40 (26.3)	36 (25.9)
Arthralgia	21 (13.8)	17 (11.2)	19 (13.7)
Osteoporosis	7 (4.6)	9 (5.9)	8 (5.8)
Nervous system	75 (49.3)	59 (38.8)	72 (51.8)
Anxiety	6 (3.9)	9 (5.9)	9 (6.5)
Depression	7 (4.6)	7 (4.6)	9 (6.5)
Dizziness	17 (11.2)	11 (7.2)	13 (9.4)
Hypesthesia	7 (4.6)	4 (2.6)	10 (7.2)
Insomnia	20 (13.2)	19 (12.5)	19 (13.7)
Paresthesia	10 (6.6)	4 (2.6)	15 (10.8)
Tremor	33 (21.7)	12 (7.9)	34 (24.5)
Respiratory system	88 (57.9)	86 (56.6)	72 (51.8)
Bronchitis	2 (1.3)	5 (3.3)	7 (5.0)
Cough increased	16 (10.5)	28 (18.4)	8 (5.8)
Dyspnea	30 (19.7)	28 (18.4)	22 (15.8)
Pharyngitis	15 (9.9)	10 (6.6)	14 (10.1)
Pneumonia	11 (7.2)	14 (9.2)	7 (5.0)
Pulmonary physical finding	19 (12.5)	19 (12.5)	12 (8.6)
Rhinitis	9 (5.9)	10 (6.6)	10 (7.2)

Table 15. Number (%) of Subjects Reporting Adverse Events by With an Overall Incidence of ≥5%

Body System[a]	Treatment		
Adverse Event	Group 1	Group 2	Group 3
	SRL/TAC	SRL/MMF	TAC/MMF
	n=152	n=152	n=139
Upper respiratory infection	26 (17.1)	19 (12.5)	25 (18.0)
Skin and appendages	60 (39.5)	63 (41.4)	60 (43.2)
Acne	19 (12.5)	14 (9.2)	3 (2.2)
Herpes zoster	4 (2.6)	7 (4.6)	7 (5.0)
Pruritus	11 (7.2)	19 (12.5)	18 (12.9)
Rash	15 (9.9)	18 (11.8)	11 (7.9)
Skin disorder	12 (7.9)	5 (3.3)	13 (9.4)
Skin ulcer	5 (3.3)	8 (5.3)	1 (0.7)
Sweating	3 (2.0)	2 (1.3)	9 (6.5)
Special senses	23 (15.1)	17(11.2)	21 (15.1)
Abnormal Vision	9 (5.9)	6 (3.9)	10 (7.2)
Urogenital system	110 (72.4)	119 (78.3)	104 (74.8)
Acute kidney failure	7 (4.6)	10 (6.6)	3 (2.2)
Albuminuria	17 (11.2)	22 (14.5)	9 (6.5)
Bladder pain	2 (1.3)	5 (3.3)	7 (5.0)
Dysmenorrhea	3 (7.0)	0	0
Dysuria	9 (5.9)	11 (7.2)	21 (15.1)
Hematuria	22 (14.5)	27 (17.8)	15 (10.8)
Impotence	1 (0.9)	6 (5.5)	2 (2.5)
Kidney function abnormal	12 (7.9)	7 (4.6)	9 (6.5)
Kidney tubular necrosis	44 (28.9)	44 (28.9)	40 (28.8)
Nocturia	2 (1.3)	4 (2.6)	8 (5.8)
Oliguria	8 (5.3)	10 (6.6)	8 (5.8)
Scrotal edema	6 (5.5)	6 (5.5)	4 (4.9)
Urinary frequency	8 (5.3)	3 (2.0)	4 (2.9)
Urinary tract disorder	9 (5.9)	13 (8.6)	7 (5.0)
Urinary tract infection	40 (26.3)	32 (21.1)	38 (27.3)

MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus.

a. Body system totals are not necessarily the sum of the individual adverse events since a subject may report ≥2 different adverse events in the same body system.

Twenty-six (26) TEAEs occurred at an incidence of >15%. Overall, the 5 most commonly reported TEAEs were peripheral edema, local reaction to procedure, anemia, diarrhea, and hypertension. AEs reported in a significantly greater number of subjects in Group 1 than in Group 3 were thrombosis, liver function test abnormal, thrombocytopenia, hyperlipidemia, peripheral edema, somnolence, and acne. Similarly, AEs reported in a significantly greater number of subjects in Group 3 than Group 1 were dysuria and diarrhea.

The incidence of infection was reported in Group 1 (93, 61.2%) and Group 3 (93, 66.9%) (p=0.33) with the most commonly reported infections reported as infection (body as a whole) and urinary tract infection in both groups. In Group 2, 97 (63.8%) subjects had infection during the study.

In addition, in Group 1, 25 (16.4%) subjects had lymphocele during the study compared with 12 (8.6%) in Group 3. The difference was not statistically significant (p=0.053). In Group 2, 28 (18.4%) subjects had lymphocele during the study.

Similarly, the incidence of malignancy was reported in Groups 1 and 3: 7 (4.6%) subjects in Group 1 and 5 (3.6%) subjects in Group 3 (p = 0.772). The most common malignancy was skin carcinoma in Group 1 (5, 3.3%) and carcinoma (body as a whole) (2, 1.4%) in Group 3. In Group 2, 5 (3.3%) subjects reported malignancy, the most common being skin carcinoma.

Serious Adverse Events (SAE): Forty eight (48) subjects experienced death, graft loss or a life-threatening infection or malignancy - excluding basal cell or squamous cell carcinoma of the skin (18 in Group 1, 18 in Group 2, 12 in Group 3). Note that a subject may have experienced one or more of these events. There were 20 deaths (8, 8 and 4 for Groups 1,2 and 3, respectively), 20 subjects with graft losses (10, 8 and 2 for Groups 1, 2 and 3 respectively), 7 subjects with malignancies (1, 2 and 4 for Groups 1, 2 and 3, respectively), and 10 subjects with life-threatening infection (1, 7 and 2 for Groups 1, 2 and 3 respectively).

Discontinuations: AEs led to discontinuation of study treatment (not necessarily from the study) for 63 (41.4%) subjects in Group 1 and 35 (25.2%) subjects in Group 3. The most frequent cause for discontinuation of study treatment was transplant rejection in Group 1 (17, 11.2%) and infection in Group 3 (11, 7.9%). Sixty-six (66, 43.4%) subjects in Group 2 were discontinued from the study treatment because of AEs. The most common AE was transplant rejection (31, 20.4%). There were more withdrawals from the study in Group 1 than Group 3 because of AEs.

Deaths: Overall, 21 subjects died in the study: 8 subjects (5.3%) in Group 1, 8 (5.3%) subjects in Group 2, and 5 subjects (3.6%) in Group 3. This includes 1 death in Group 3 during the follow-up month after the last dose of the study drug; this subject was included here for completeness but was not included in the 2-year analysis of efficacy.

Laboratory Evaluations: Most of the laboratory parameters were comparable among the 3 groups. In general, the lipid profile in Group 3 was significantly better than that in Group 1. The liver function tests (aspartate aminotransferase and alanine aminotransferase) in Group 1 were significantly higher than those in Group 3 at most time points.

CONCLUSIONS: Treatment with SRL+TAC withdrawal was comparable with TAC+IMPDH inhibitor with similar renal function, acute rejection, and subject survival at 1 and 2 years. However, a higher rate of graft loss and a higher rate of discontinuation due to AEs were observed in the SRL+TAC withdrawal group. Treatment with SRL+IMPDH inhibitor was associated with a higher rate of acute rejection, and therefore, this treatment regimen was terminated by the Sponsor. This finding is consistent with previous study (NCT00137345) that included a similar treatment regimen. Despite a higher rate of acute rejection in the SRL+IMPDH inhibitor group, similar renal function was observed compared with treatment with TAC+IMPDH inhibitor at 1 year. Because of early termination of this treatment regimen, the 2-year data were difficult to interpret. However, based on the available 2-year data, graft and subject survivals in SRL+IMPDH inhibitor group were not significantly different than in TAC+IMPDH inhibitor group.