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

PROTOCOL NO.: 0468H1-318-WW (B1741188)

PROTOCOL TITLE: 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

Study Centers: A total of 68 centers took part in the study; 20 in the United States of America, 7 in Argentina, 6 in Australia, 5 in Spain, 4 in Italy, 3 each in Hungary and Turkey, 2 each in France, Greece, Canada, the Republic of Korea, South Africa, the United Kingdom, and 1 each in Chile, Cyprus, Norway, Poland, Portugal, Singapore, Sweden, Taiwan.

Study Initiation and Final Completion Dates: June 2005 to June 2006

This study was halted prematurely on 06 June 2006 at the request of the Sponsor because of safety concerns associated with significantly greater rates of biopsy confirmed acute rejection in subjects treated with sirolimus compared with those receiving cyclosporine (CsA), despite the additive effects of basiliximab, mycophenolate mofetil (MMF), and corticosteroids.

Phase of Development: Phase 3

Study Objectives:

Primary Efficacy Objectives:

- To demonstrate superiority of the sirolimus regimen versus (vs) the CsA regimen by intent-to-treat (ITT) analysis of renal function at 52 weeks, measured by mean calculated glomerular filtration rate (GFR; Nankivell method). The ITT population was defined as all subjects who were randomly assigned to study therapy and underwent transplantation.

Primary Safety Objectives:

- To demonstrate non-inferiority at 52 weeks in the composite endpoint of the incidence of first occurrence of graft loss or death. The safety population was defined as subjects who received at least 1 dose of study medication.

Secondary Efficacy Objectives:

- Incidence of the first occurrence of biopsy-confirmed acute rejection (BCAR) at 12, 24, 52, 104, 156 and 208 weeks.
- Histologic grade of severity of BCAR at 12, 24, 52, 104, 156 and 208 weeks.
- Mean on-therapy calculated Nankivell GFR at 24, 52, 104, 156 and 208 weeks.
- Mean Nankivell GFR at 24, 104, 156 and 208 weeks for all randomly assigned subjects in both groups (ITT).
- Slopes of 1/creatinine vs time at 24, 52, 104, 156 and 208 weeks (ITT and on-therapy).
- Slopes of Nankivell GFR vs time at 24, 52, 104, 156 and 208 weeks (ITT and on-therapy).
- Mean GFR as measured by radionuclide or comparable methodology at 24, 52, and 104 weeks (on-therapy, at centers that elected to participate).
- Progression of chronic allograft nephropathy (CAN) at 52 weeks (protocol-mandated biopsies at centers that elected to participate).
- Quality of life (QoL) outcomes at 24, 52, and 104 weeks.

Secondary Safety Objectives:

- Incidence of subjects and graft survival at 12, 24, 104, 156 and 208 weeks.
- Mean systolic and diastolic blood pressure (BP) at 52 and 104 weeks.
- Incidence of infection at 52 and 104 weeks.
- Incidence of malignancy (including histologically confirmed lymphoproliferative disease) at 52, 104, and 208 weeks.
- Incidence of delayed graft function (DGF), defined as the need for dialysis within the first 7 days after transplantation. Recovery from DGF was defined as the absence of the need for dialysis for 7 days after the last dialysis treatment. Duration of DGF was defined as the number of days from date of transplantation to last dialysis.
- Incidence of wound-healing complications defined as Class 1 (required surgical closure, repair) and Class 2 (did not require surgical repair).
- Incidence of post-transplant diabetes mellitus (PTDM), defined as the requirement for new insulin use for >30 consecutive days after transplantation.

- Cumulative use of lipid-lowering agents at 52 and 104 weeks.
- Cumulative use of antihypertensive medications at 52 and 104 weeks.
- Incidence of other treatment-emergent adverse events (TEAEs).
- Incidence of anemia and use of recombinant erythropoietic agents at 12, 24 and 52 weeks.

METHODS

Study Design:

This was an open-label, randomized, parallel-group, comparative study in de novo renal transplant recipients. Subjects were randomly assigned in a 2:1 ratio to either of 2 treatment groups (Group A: sirolimus, basiliximab, MMF, and corticosteroids; or Group B: CsA, basiliximab, MMF, and corticosteroids) before transplantation. Subjects were stratified prospectively by race (Black vs Non-Black) and donor source (living related, living unrelated, or deceased).

Approximately 500 subjects were to participate in this study out of which 333 subjects were to be randomly assigned to Group A and 167 subjects were to be randomly assigned to Group B. Subjects withdrawn from the study were not to be replaced, regardless of the reason for withdrawal.

This study was to be completed in approximately 60 months (260 weeks), which included an approximately 52 week enrollment period, a 104 week treatment period, and a 104 week follow-up period. The end of the study was to be the last visit of the last subject.

Table 1 shows the study flowchart for subjects who completed 104 weeks of treatment. Table 2 shows the study flowchart for subjects who discontinued use of study medication before completing 104 weeks of randomly assigned treatment. Subjects were to return for follow-up evaluations as described in the study flowcharts. Subjects were to be evaluated for the primary study endpoint after 52 weeks of therapy but were to continue to receive their randomized therapy for up to 104 weeks.

Early in the study, a significantly increased rate of BCAR was observed in the group receiving sirolimus; the protocol was amended to increase the loading dose of sirolimus. The study was halted prematurely by the Sponsor on 06 June 2006 because of safety concerns – a significantly greater rate of acute rejection episodes and a numerically higher rate of death in the group receiving sirolimus, despite adequate sirolimus trough levels that were present in subjects receiving the new dosing regimen under study amendment 2.

Table 1. Study Flowchart of Subjects Who Completed 104 Weeks of Treatment

	Study Week After Transplant																				
	S/B[a]	**Day of Trans**	**Within 48 h After Trans**[b]	**1**[c]	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**42**	**52**	**64**	**76**	**88**	**104**	**108 F/U**	**156 F/U**	**208 F/U**
Study Visit Window (Days)				**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±12**	**±12**	**±30**	**±30**
Informed consent[d]	X																				
Basiliximab therapy, Group A and Group B[e]		X		X																	
Corticosteroids, MMF therapy, Group A and Group B		X	X[b]	X----------X																	
SRL administration (SRL therapy, Group A)			X[b]	X----------X																	
CsA administration (CsA therapy, Group B)			X[b]	X----------X																	
Medical history	X																				
Concomitant medications[f]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs monitoring[g]	X	X	X	X----------X																	
Physical examination	X		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs, weight[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[i]	X										X			X				X			
Hematology[j]	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X			
Lipid levels, glucose (fasting)[k]	X		X	X			X	X	X		X			X		X		X	X		
Blood chemistry values[l]	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X			
Serum creatinine and BUN[m]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Random AM urine collection or protein and creatinine concentration[n]				X			X				X			X				X			
Measured GFR (radionuclide or comparable technique) at centers that elected to participate											X			X				X			
Pregnancy test[o]	X			When clinically indicated																	

Table 1. Study Flowchart of Subjects Who Completed 104 Weeks of Treatment

	Study Week After Transplant																			
	S/B[a]	**Day of Trans**	**Within 48 h After Trans[b]**	**1[c]**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**42**	**52**	**64**	**76**	**88**	**104**	**108 F/U**	**156 F/U**	**208 F/U**
Study Visit Window (Days)				**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±12**	**±12**	**±30**	**±30**
CMV antibody (IgG) test[p]	X										X			X				X			
SRL trough blood levels (SRL therapy group only)[q]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CsA trough blood levels (CsA therapy group only)[r]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
MPA/MPAG trough plasma levels (both treatment groups)[s]				X			X		X		X			X							
Renal biopsy (centers electing to participate)[t]			X											X							
DGF assessment[u]					X				X												
Wound healing assessment							X		X												
Acute rejection assessment									X		X			X				X		X	X
Subject survival and graft survival									X		X			X				X		X	X
QoL[v]	X										X			X				X			

AE = adverse event; B = baseline; BUN = blood urea nitrogen; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CRF = case report form; CsA = cyclosporine; DGF = delayed graft function; F/U = follow-up; GFR = glomerular filtration rate; HDL = high-density lipoprotein; IgG = immunoglobulin G; IV = intravenously; LDL = low-density lipoprotein; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MPAG = mycophenolic acid glucuronide; QoL = quality of life; S = screening; SAE = serious adverse event; SRL = sirolimus; TG = triglycerides; Trans = transplantation.

a. S/B: up to 7 days before transplantation.
b. Study medication (SRL, CsA, MMF, corticosteroids) could have been given after the subject was randomly assigned to test article and before transplantation (up to 7 days before transplantation) in centers where pre-transplant treatment was utilized. SRL or CsA evaluations on the first day of dose administration were performed before test article administration. Clock times were collected for administration of the first SRL dose, administration of first CsA dose, AEs occurring on that day, and laboratory values obtained on that day.
c. Subjects must have taken the first dose of study medication by this study visit (Week 1).
d. Informed consent was obtained before any study procedure was performed.
e. Basiliximab was administered IV on the day of transplantation and on Day 4 after surgery. The second dose of basiliximab may have been administered on Day 3 after surgery if the subject was discharged on Day 3.
f. Limited information about concomitant medications was collected at Weeks 156 and 208; SRL and CNI records were collected at these times.
g. AE monitoring: screening through Week 108. Limited AE monitoring occurred at Follow-up Weeks 156 and 208. Limited AE monitoring included graft loss, death, and

Table 1. Study Flowchart of Subjects Who Completed 104 Weeks of Treatment

	Study Week After Transplant																				
	S/B[a]	Day of Trans	Within 48 h After Trans[b]	1[c]	2	3	4	8	12	16	24	32	42	52	64	76	88	104	108 F/U	156 F/U	208 F/U
Study Visit Window (Days)				±2	±2	±2	±2	±2	±7	±7	±14	±14	±14	±14	±14	±14	±14	±12	±12	±30	±30

malignancy; acute rejection episodes were also reported. Of note, any of these limited AEs (excluding hospitalizations) that met any of the criteria for an SAE must also have been reported on the appropriate Sponsor Research form within the standard time period for that SAE.

h. Vital signs: blood pressure, heart rate, and temperature (oral, axillary, or tympanic). Weight was to be obtained at all study visits and at the time of any acute deterioration in renal function.

i. Height was collected at all specified time points for subjects who were 14 to 19 years of age. All other subjects required height measurement collected at S/B only.

j. Hematology: complete blood count, 5-part differential, and platelet count.

k. Fasting blood chemistry (8 to 12 hours): cholesterol (total, LDL, and HDL), TG, and serum glucose. If fasting lipids could not have been obtained before randomization, they could have been performed after subject was randomly assigned to test article.

l. Blood chemistry.

m. Creatinine and BUN.

n. Random morning urine void for protein and creatinine concentrations. Of note, the first morning urine void could not be used for this laboratory determination.

o. Pregnancy test: qualitative serum for all female subjects at risk for pregnancy. If pregnancy occurred, test article use was discontinued for the subject and monitoring for AEs was continued for 12 weeks after discontinuation.

p. Only for CMV-negative subjects; not necessary to repeat if the subject became CMV positive.

q. SRL trough blood levels (SRL therapy group subjects only): before dosing and 24±2 hours after the last SRL dose, every 5 to 7 days after initiation of SRL (until SRL levels were ≥10 ng/mL), after all SRL dose adjustments, and whenever possible on the day of any treatment-related AE or unexplained deterioration in renal function (including suspected acute rejection). May have been monitored more frequently at the discretion of the Investigator.

r. CsA trough blood levels (CsA therapy group subjects only): before dosing in the morning and 12±2 hours after the last CsA dose, after all CsA dose adjustments, and whenever possible on the day of any treatment-related AE (including acute rejection) or unexplained deterioration in renal function. May have been monitored more frequently at the discretion of the Investigator.

s. MPA/MPAG trough plasma levels were not available for concentration-controlled adjustment of dosing. MPA/MPAG levels were collected on the day of acute rejections in addition to specified visits.

t. The renal biopsy for the specimen required within 48 hours after transplantation may have been obtained from the explanted kidney at the time of transplantation.

u. DGF was defined as the need for dialysis within the first 7 days after transplantation; recovery from DGF was defined as the absence of the need for dialysis for 7 days after the last dialysis treatment.

v. S/B QoL CRFs could have been completed at any time up until the time of discharge from the hospital after transplantation.

Table 2. Study Flowchart of Randomly Assigned Subjects Who Discontinued Study Medication Before Completing 104 Weeks of Treatment

	Time of Dis. (Within 1 Week of Dis.)	4 Weeks After Dis.	12 Weeks After Study Entry	24 Weeks After Study Entry	52 Weeks After Study Entry	104 Weeks After Study Entry	156 Weeks After Study Entry	208 Weeks After Study Entry
Study Visit Window (Days)	**±7**	**±14**	**±7**	**±14**	**±14**	**±12**	**±30**	**±30**
Physical examination	X	X						
Vital signs, weight[a]	X	X		X	X	X	X	X
Height[b]				X	X	X		
AEs monitoring[c]	X	X	X	X	X	X	X	X
Concomitant medications[d]	X	X	X	X	X	X	X	X
Hematology laboratory values[e]	X	X	X					
Lipid levels, glucose (fasting)[f]	X	X		X	X	X		
Blood chemistry values	X	X	X					
Creatinine and BUN[g]	X	X	X	X	X	X	X	X
Measured GFR (radionuclide or comparable technique) at centers that elected to participate					X	X		
Pregnancy test[h]	When clinically indicated							
Random AM urine collection for protein and creatinine concentration[i]	X			X	X	X		
SRL trough levels (SRL subjects only)	X							
CsA (CsA subjects only)	X							
Acute rejection assessment	X		X	X	X	X	X	X
Subject survival and graft survival	X		X	X	X	X	X	X
Wound healing assessment		X[j]	X					
DGF assessment		X[j]	X					
QoL Outcome	X			X	X	X		

AE = adverse event; BUN = blood urea nitrogen; CNI = calcineurin inhibitors; CRF = case report form; CsA = cyclosporine; Dis. =discontinuation; DGF = delayed graft function; GFR = glomerular filtration rate; HDL = high-density lipoprotein;LDL = low-density lipoprotein; QoL = quality of life; SAE = serious adverse event; SRL = sirolimus; TG = triglycerides.

a. Weight and vital signs (sitting blood pressure and heart rate) at all visits. Temperature (oral, axillary, or tympanic) not required at Weeks 24, 52, and 104 after study entry.

b. Height was collected at all specified time points for subjects who were 14 to 19 years of age. All other subjects required height measurement collected at

Table 2. Study Flowchart of Randomly Assigned Subjects Who Discontinued Study Medication Before Completing 104 Weeks of Treatment

Screening/Baseline only.

c. AE monitoring: at the time of discontinuation from randomized treatment and through 4 weeks after discontinuation. Limited AE monitoring through Week 104 (to include: graft loss, death or life-threatening event, infection, malignancy, hospitalization, dialysis) and episodes of acute rejections were also reported. At Weeks 156 and 208 limited AE monitoring included, graft loss, death, and malignancy, and episodes of acute rejections were also reported. Of note, any of these limited AEs (excluding hospitalization) that met any of the criteria for an SAE must also have been reported on the appropriate Sponsor Research form within the standard time period for that SAE.
d. Limited concomitant medications were to be collected. At time of discontinuation, study medication, as well as concomitant immunosuppressive agents, lipid lowering agents, antihypertensive agents, erythropoietic agents, and insulin were to be collected. At 4 weeks after discontinuation, and at Weeks 12, 24, 52, and 104 after study entry the following were collected: concomitant immunosuppressive agents, lipid lowering agents, antihypertensive agents, erythropoietic agents, and insulin. At 156 and 208 weeks after study entry, concomitant immunosuppressives (SRL and CNI only) were collected.
e. Hematology: complete blood count, 5-part differential, and platelet count.
f. Fasting blood chemistries (8 to 12 hours): cholesterol (total, LDL, and HDL), TG, and serum glucose.
g. Creatinine, BUN, and blood chemistries.
h. Pregnancy test: qualitative serum for all female subjects at risk for becoming pregnant. If a pregnancy occurred, subject discontinued study drug and monitoring for AEs continued for 12 weeks after discontinuation.
i. Random morning urine void for protein and creatinine concentrations. Of note, the first morning urine void could not be used for this laboratory determination.
j. Wound healing assessment and DGF assessment CRFs were to be completed at 4 weeks after discontinuation visit only if subject discontinued before completing the Study Week 4 Visit.

Number of Subjects (Planned and Analyzed): Approximately 500 subjects were planned for participation (approximately 333 subjects were to be randomly assigned to Group A and 167 subjects were to be randomly assigned to Group B). It was estimated that approximately 550 subjects would be screened to enroll the target 500 subjects.

A total of 487 subjects were enrolled and randomly assigned in a 2:1 ratio to either Group A (319 subjects) or Group B (168 subjects). Among these subjects, 475 underwent transplantation and composed the ITT population (314 in Group A and 161 in Group B). There were 471 subjects (310 subjects in Group A and 161 subjects in Group B) who received at least 1 dose of study medication and therefore composed the safety population.

Diagnosis and Main Criteria for Inclusion and Exclusion: Subjects, aged >13 years (>18 years in some regions, per local regulations) and weight >40 kg, subjects with end-stage renal disease who received a primary renal allograft from a deceased donor, a living unrelated donor, or an human leukocyte antigen (HLA) mismatched living related donor, or subjects who received a primary transplant before the initiation of maintenance dialysis, where the calculated GFR (Nankivell) of the native kidney(s) must have been <20 mL/min within 24 hours before transplantation from a deceased donor, a living unrelated donor, or an HLA-mismatched living related donor, were included in the study.

Main Exclusion Criteria: Subjects were excluded for any of the following: receipt of a kidney from a deceased donor aged >60 years or from a living donor aged >65 years or from a donor aged 50 to 60 years having 2 of the following, terminal creatinine level >1.5 mg/dL (132 μmol/L), death secondary to cerebral vascular accident, or known history of hypertension requiring medical treatment; receipt of a kidney from an HLA-identical living related donor; had a previous solid organ transplant; had received pediatric en bloc or dual adult kidney transplants; total donor kidney ischemia time >30 hours; receipt of kidneys from non-heart-beating donors; or known or suspected malignancy within 5 years before enrollment.

Study Treatment:

Subjects randomly assigned to Group A received a regimen of sirolimus, basiliximab, MMF, and corticosteroids; subjects randomly assigned to Group B received a regimen of CsA, basiliximab, MMF, and corticosteroids.

Sirolimus: Oral tablets (1, 2, and 5 mg), oral solution (1-mg/mL concentrate); dose was dependent upon target trough concentrations and was adjusted to maintain the required trough concentration ranges. The target whole blood sirolimus trough concentrations are presented in Table 3.

After being randomly assigned to Group A, each subject who began sirolimus dosing after transplantation received an initial sirolimus 15 mg oral loading dose within 24 hours after transplantation. During the second 24 hours after transplantation, these subjects received a second 15 mg oral loading dose. Beginning on the third day after transplantation, they received 10 mg daily until their whole blood sirolimus trough levels were ≥10.0 ng/mL (high-performance liquid chromatography equivalent).

For subjects who began sirolimus dosing before transplantation, no sirolimus loading doses were required. These subjects received a 10 mg dose of sirolimus within 24 hours after transplantation and continued to receive sirolimus 10 mg daily until their whole blood sirolimus trough levels were ≥10.0 ng/mL after which subsequent doses were adjusted to maintain trough levels within the protocol-specified range.

Table 3. Target Whole Blood Sirolimus Trough Concentration Ranges

Intervals	Sirolimus	
	HPLC	Immunoassay[a]
Study start to Week 13	10 to 15 ng/mL	12 to 18 ng/mL
Week 14 to Week 26	10 to 15 ng/mL	12 to 18 ng/mL
Week 27 to Week 104	8 to 15 ng/mL	10 to 18 ng/mL

C_{HPLC} = concentration of sirolimus by high-performance liquid chromatography; C_{IMx} = concentration of sirolimus by immunoassay; HPLC = high-performance liquid chromatography.

a. The formula for conversion of HPLC values to immunoassay values was: $C_{IMx} = (1.23 \times C_{HPLC}) - 0.20$.

Cyclosporine (CsA): After randomization, Group B subjects received 6 to 8 mg/kg of CsA as an oral loading dose (Neoral only), in divided doses, initiated between 7 days before and 48 hours after transplantation. Whole blood CsA trough concentrations ranges were monitored at designated intervals and the twice-daily CsA maintenance dose was adjusted to maintain the desired trough concentration ranges presented in Table 4.

Table 4. Target Whole Blood Cyclosporine Trough Concentration Ranges

Intervals	Trough Concentration Range
Study start to Week 13	150 to 300 ng/mL
Week 14 to Week 26	50 to 200 ng/mL
Week 27 to Week 104	50 to 150 ng/mL

Basiliximab, Mycophenolate Mofetil, and Corticosteroid Dosing in Both Groups: Dosages and times of dose administrations of basiliximab, MMF, and corticosteroids are presented in Table 5.

Table 5. Basiliximab, Mycophenolate Mofetil, and Corticosteroid Dosage and Administration for Both Treatment Group A and Treatment Group B

Time of Dose Administration	Basiliximab	MMF	Corticosteroids
Within 2 hours before transplantation	20 mg (IV)		
Three (3) to 4 days after transplantation	20 mg (IV)		
Within 48 hours after transplantation		Total dose up to 2 g/day[a]	
Duration of treatment		Minimum of 1 g/day[b]	
Day of transplantation (for 2 days)[c]			500 mg methyl prednisolone (IV)
Day 3 through Day 7			Tapered from 120 mg to a minimum of 30 mg (IV methylprednisolone or oral prednisone)
Day 8 through Day 30			Tapered to a minimum of 20 mg
Day 31 through Week 12			Tapered 2.5 mg every 2 weeks to achieve a minimum of 10 mg/day
Week 13 through Week 24			Minimum of 7.5 mg/day or equivalent every other day
Week 25 through Week 52			Minimum of 5 mg/day or equivalent every other day[d]

IV = intravenous; MMF = mycophenolate mofetil.

a. Different for sirolimus when trough was therapeutic level (2 g/day if sirolimus <10 ng/mL; 1.5 g/day if sirolimus ≥10 ng/mL).
b. Further dose reductions were to be discussed with the Study Medical Monitor. MMF administration may have been withheld for up to 7 days; however, if MMF was withheld for >7 continuous days, the subject was permanently withdrawn from his or her respective therapy group, unless otherwise approved by the Study Medical Monitor.
c. Corticosteroids could have been administered up to 48 hours before transplantation in centers where this was local practice.
d. If centers desired, and if the subject did not have an acute rejection, the dose of corticosteroids could have been reduced further, after Week 52, to 2.5 mg/day.

A 20 mg dose of basiliximab was administered intravenously (IV) within 2 hours before transplantation and a second 20 mg dose was administered IV on Day 4 after transplantation; the second dose of basiliximab may have been administered on Day 3, if the subject was discharged on Day 3.

MMF was administered throughout the duration of the treatment period. In treatment Group A, the MMF dose should have been reduced to 1.5 g/day once the sirolimus trough level was ≥10 ng/mL. Additional dose reduction of MMF was permitted if not well tolerated; a minimum daily dose of 1 g/day was required, unless approved by the Medical Monitor. If MMF administration was withheld for >7 continuous days the subject was permanently withdrawn from the sirolimus therapy group unless approved by the Medical Monitor.

Corticosteroids could have been administered up to 48 hours before transplantation with a reduction in the dose to a minimum of 7.5 mg/day (or the equivalent every other day) by

6 months. The minimum required dose (or the equivalent every other day) was 5 mg/day from 6 months until the end of the study and could be further reduced to a minimum of 2.5 mg/day after 12 months if no acute rejection had occurred.

Subjects were to participate in the study for approximately 48 months (208 weeks). This included a 7 day screening period, a 104 week treatment period, and a 104 week follow-up period. Subjects who discontinued from randomized therapy before completing 104 weeks of therapy were to remain in the study until all follow-up evaluations were performed. After study termination, all subjects were followed for up to 2 months. Overall, subjects were followed for a mean of 190 days (minimum 5 days, maximum 441 days). There were no differences between groups.

Efficacy and Safety Endpoints:

Primary Efficacy Endpoint:

- Renal function at 52 weeks, as measured by mean calculated GFR (Nankivell).

Primary Safety Endpoint:

- Composite endpoint of the incidence of the first occurrence of graft loss (functional loss necessitating maintenance dialysis for >56 days or physical loss due to nephrectomy or re-transplantation) or death at 52 weeks.

Secondary Efficacy Endpoints:

- First occurrence of BCAR at 12, 24, 52, 104, 156, and 208 weeks.
- Histologic grade of severity of BCAR at 12, 24, 52, 104, 156, and 208 weeks.
- Mean on-therapy calculated Nankivell GFR at 24, 52, 104, 156, and 208 weeks.
- Mean Nankivell GFR at 24, 104, 156, and 208 weeks for all randomly assigned subjects in both treatment groups (ITT population).
- Slopes of 1/creatinine vs time at 24, 52, 104, 156, and 208 weeks (ITT and on-therapy populations).
- Slopes of Nankivell GFR vs time at 24, 52, 104, 156, and 208 weeks (ITT and on-therapy populations).
- Mean GFR, as measured by radionuclide or comparable methodology, at 24, 52, and 104 weeks (on-therapy population; at centers that elected to participate).
- Progression of CAN at 52 weeks (protocol-mandated biopsies at centers that elected to participate).
- QoL outcomes at 24, 52, and 104 weeks.

Secondary Safety Endpoints:

- Incidence of subject survival and graft survival at 12, 24, 104, 156, and 208 weeks.
- Mean systolic and diastolic BP at 52 and 104 weeks.
- Incidence of infection at 52 and 104 weeks.
- Incidence of malignancy (including histologically confirmed lymphoproliferative disease) at 52, 104, and 208 weeks.
- Incidence of DGF, defined as the need for dialysis within the first 7 days after transplantation. Recovery from DGF was defined as the absence of the need for dialysis for 7 days after the last dialysis treatment. Duration of DGF was defined as the number of days from the date of transplantation to the last dialysis.
- Incidence of wound-healing complications, defined as Class 1 (required surgical closure, repair) and Class 2 (did not require surgical repair), evaluated on Day 21 after transplantation.
- Incidence of PTDM, defined as the requirement for new insulin use for >30 consecutive days after transplantation.
- Cumulative use of lipid-lowering agents at 52 and 104 weeks.
- Cumulative use of antihypertensive medications at 52 and 104 weeks.
- Incidence of other TEAEs.
- Incidence of anemia and use of recombinant erythropoietic agents at 12, 24, and 52 weeks.

Safety Evaluations: Safety measurements included physical examination, height, weight, and vital signs (including BP, heart rate, and temperature); complete blood count with 5 part differential and platelet count; blood chemistry, fasting lipids and serum glucose, cytomegalovirus (CMV) antibody test, and monitoring of concomitant medications.

Statistical Methods: The ITT group was defined as all subjects who were randomly assigned to study therapy and underwent transplantation.

The safety population was defined as subjects who received at least 1 dose of study medication.

Because the study was halted prematurely, certain planned analyses were not performed. These include assessment of those efficacy and safety endpoints at study-defined time points that occurred after the time of termination. Those statistical analyses that were performed include:

- Kaplan-Meier analyses for graft survival, subject survival, and BCAR-free survival. The statistical significance of the differences between groups was analyzed by the Log-rank test. For each analysis, an event was defined as graft loss, death, or BCAR. Subjects were censored if they withdrew from the study without having a qualifying event (graft loss, death, or BCAR) or if they completed the study without having an event.

- Comparison of severity of BCAR between treatment groups using the Cochran-Mantel-Haenszel (CMH) row-mean test.

- The on-therapy calculated Nankivell GFR observed mean values for all subjects in both treatment groups at those visits performed during study therapy.

- Comparison of the incidence of DGF between treatment groups using the Fisher exact test. The analysis was performed for 2 populations: all subjects and subjects who received a transplanted organ from a deceased donor.

- Comparison of the time to recovery from DGF between treatment groups using the Wilcoxon rank sum test, since all analyzed subject recovered. Recovery from DGF was defined as occurring on the last day of dialysis after the qualifying initial dialysis. Subjects whose dialysis was discontinued in <56 days were scored as recovering from DGF. For these subjects, the time to recovery was defined as the interval from the date of transplantation to the date of recovery. If a subject died or had a nephrectomy within 3 days after the last dialysis treatment, the subject was considered not recovered from DGF. A subject who withdrew from the study within the first 60 days after transplantation and whose last dialysis treatment was ongoing was excluded from the analysis because his or her recovery from DGF could not be determined.

- Data concerning wound healing were collected during Weeks 4 and 12 and were classified by the need for surgical intervention. The percentage distribution across the 3 outcomes was calculated for each treatment group and the statistical significance of the differences in distribution was assessed using the CMH row mean score test. Wounds were considered healed (all suture material removed within 3 weeks) or non-healed. Non-healed wounds were classified as Grade 1 (required surgical intervention) or Grade 2 (healed after 3 weeks without surgical intervention). For those subjects whose wound was not healed at Week 4 and whose 12 week follow-up assessment was not completed because the study was prematurely halted, wound healing was classified as Grade 2 (without surgical intervention).

- Adjusted means for systolic and diastolic BP were calculated at selected visits. The statistical significance of difference between the treatment groups for the BP was assessed by analysis of covariance with treatment as factor and respective baseline BP as covariate.

- The incidence of PTDM was assessed by examining the percentage of subjects receiving insulin before and after transplantation.

- Incidence of anemia and use of recombinant erythropoietic agents were evaluated by examining overall erythropoietic agent use and hematology values.

RESULTS

Subject Disposition and Demography: A total of 487 subjects were enrolled in the study; 319 subjects were randomly assigned to sirolimus treatment (Group A) and 168 subjects were randomly assigned to CsA treatment (Group B). There were 12 subjects who did not receive a transplanted kidney or withdrew consent before the transplantation and were excluded from all analyses. A total of 475 subjects received transplants; 314 subjects were randomly assigned to sirolimus treatment (Group A) and 161 subjects were randomly assigned to CsA treatment (Group B); these subjects composed the ITT population (all subjects randomly assigned to study medication and receiving a transplant). These subjects were further stratified by race (Black vs Non-Black) and by donor source (living vs deceased).

There were 471 subjects in the safety population, 310 (65.8%) subjects were randomly assigned to Group A (sirolimus regimen) and 161 (34.2%) subjects to Group B (CsA regimen). Table 6 summarizes the primary reasons for discontinuation from treatment for the safety population during the study period.

Table 6. Study Number (%) of Subjects Who Discontinued From the Study During the Treatment Period of the Study, by Primary Reason for Discontinuation and Treatment Group: Safety Population

Primary Reason for Discontinuation, n (%)[a]	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Total (N=471)	Group A vs Group B p-Value[b]
Total	310 (100)	161 (100)	471 (100)	
Discontinuation of study by Sponsor	213 (68.7)	134 (83.2)	347 (73.67)	<0.001***
Adverse event	54 (17.4)	11 (6.8)	65 (13.8)	0.001**
Unsatisfactory response (efficacy)	32 (10.3)	7 (4.4)	39 (8.3)	0.033*
Subject request	4 (1.3)	2 (1.2)	6 (1.3)	1.000
Death	3 (1.0)	1 (0.6)	4 (0.9)	1.000
Other	3 (1.0)	3 (1.9)	6 (1.3)	0.416
Investigator request	1 (0.3)	1 (0.6)	2 (0.4)	1.000
Lost to follow-up	0	1 (0.6)	1 (0.2)	0.342
Protocol violation	0	1 (0.6)	1 (0.2)	0.342

CsA = cyclosporine; N = total number of subjects; n = number of subjects in each treatment group; SRL = sirolimus; vs = versus.

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

b. Overall p-value: Fisher exact test, p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Table 7 presents demographic and baseline characteristics for all randomly assigned subjects.

Table 7. Demographic and Baseline Characteristics, Recipients: ITT Population

Characteristic	Group A SRL Regimen (n=314)	Group B CsA Regimen (n=161)	Total (N=475)	Group A vs Group B p-Value
Sex, n (%)				0.554[a]
Female	96 (30.6)	45 (28.0)	141 (29.7)	
Male	218 (69.4)	116 (72.1)	334 (70.3)	
Ethnic origin, n (%)				0.291[a]
White	245 (78.0)	127 (78.9)	372 (78.3)	
Black	25 (8.0)	13 (8.1)	38 (8.0)	
Asian	16 (5.1)	6 (3.7)	22 (4.6)	
Other	15 (4.8)	11 (6.8)	26 (5.5)	
Hispanic	13 (4.1)	4 (2.5)	17 (3.6)	
Age, years	314	161	475	
Mean	42.9	42.7	42.9	0.876[b]
Primary etiology of renal failure, n (%)				0.450[a]
Autoimmune disease, systemic	5 (1.6)	5 (3.1)	10 (2.1)	
Diabetes mellitus	23 (7.3)	13 (8.1)	36 (7.6)	
Glomerulonephritis	64 (20.4)	27 (16.9)	91 (19.2)	
Hypertension	38 (12.1)	18 (11.3)	56 (11.8)	
IgA nephropathy (Berger disease)	37 (11.8)	12 (7.5)	49 (10.3)	
Interstitial nephritis/ pyelonephritis	18 (5.7)	6 (3.8)	24 (5.1)	
Obstructive uropathy/reflux	20 (6.4)	12 (7.5)	32 (6.8)	
Polycystic kidney disease	28 (8.9)	28 (17.5)	56 (11.8)	
Other	79 (25.2)	35 (21.7)	114 (24.0)	
Unknown	2 (0.6)	3 (1.9)	5 (1.1)	
Missing	0	1 (0.6)	1 (2.1)	
HLA mismatches, n (%)				0.663[a]
0	12 (3.8)	5 (3.1)	17 (3.6)	
1	16 (5.1)	11 (6.9)	27 (5.7)	
2	51 (16.2)	32 (20.0)	83 (17.5)	
3	101 (32.2)	46 (28.8)	147 (31.0)	
4	56 (17.8)	28 (17.5)	84 (17.7)	
5	43 (13.7)	27 (16.9)	70 (14.8)	
6	34 (10.8)	11 (6.9)	45 (9.5)	
Unknown	1 (0.3)	0	1 (0.2)	
Missing	0	1	1	
PRA status, n	280	143	423	0.089[b]
Mean	0.9	2.8	1.5	
Missing	34	18	52	

ANOVA = analysis of variance; CsA = cyclosporine; HLA = human leukocyte antigen; IgA = immunoglobulin A; ITT = intent-to-treat; N = number of subjects; n = number of subjects in each specific criteria; PRA = panel-reactive antibody; SRL = sirolimus; vs = versus.

a. Fisher exact test p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

b. One-way ANOVA with treatment as factor.

The mean age of donors in both treatment groups was approximately 41 years. In both treatment cohorts, the majority of donors were male and White. In both treatment groups, the mean organ ischemia time was approximately 11 hours and the sources of most grafts were

deceased donors. Approximately 79% and 73% of subjects in Groups A and B, respectively, were positive for CMV by immunoglobulin G status, a difference that was statistically significant (p=0.012).

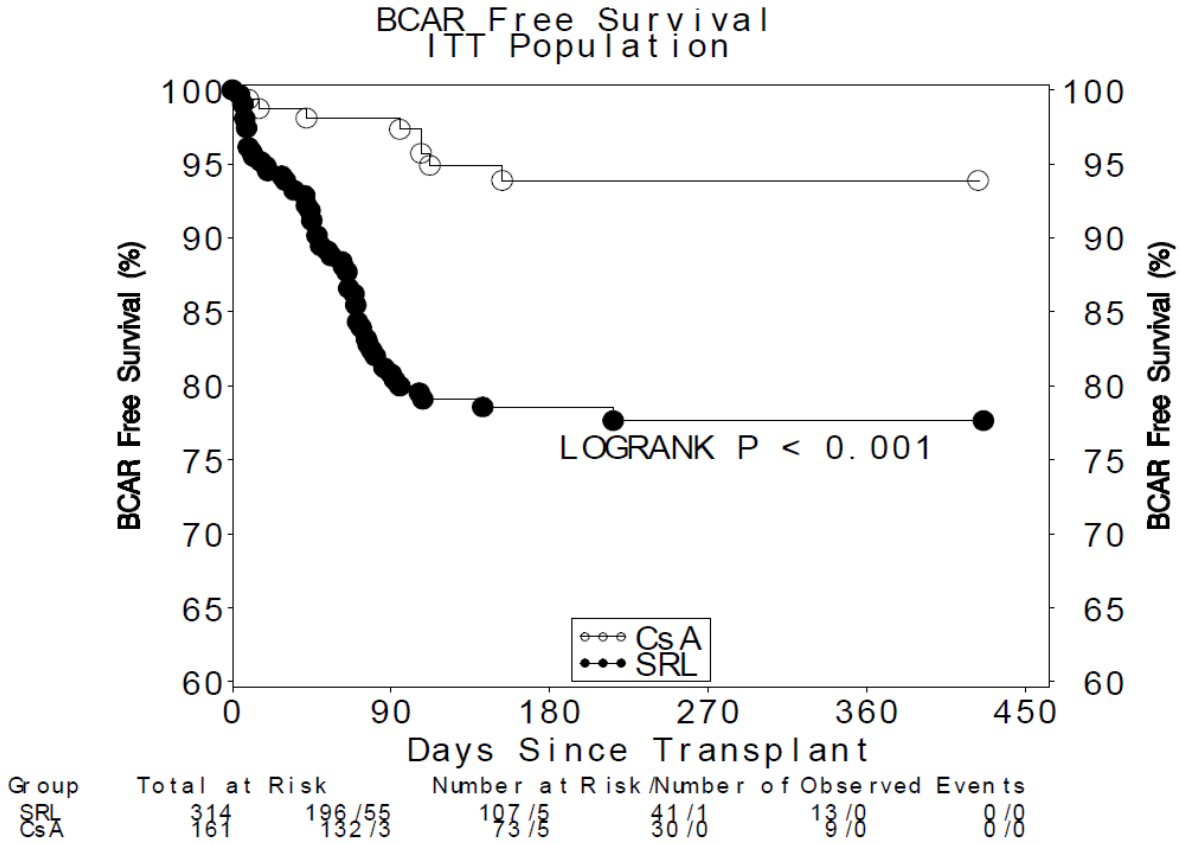
Efficacy Results:

Primary Endpoint - Renal Function: The primary efficacy endpoint was renal function, as measured by Nankivell calculated GFR, planned for Week 52 using ITT analysis. As the study was terminated early, this analysis was not performed.

Secondary Endpoints:

Biopsy-Confirmed Acute Rejection: Acute rejection was confirmed by biopsy (Banff 1997 Grade 1, 2, 3, or antibody-mediated), as interpreted by the local pathologist. The time to first BCAR is presented in Figure 1. The difference in the percentage of BCAR-free survival between treatment groups was statistically significant (p <0.001), favoring Group B. The rates of BCAR-free survival at 3 months were 81% in Group A and 98% in Group B. There were 61 of 314 (19.4%) subjects with BCAR in Group A and 8 of 161 (5.0%) subjects with BCAR in Group B.

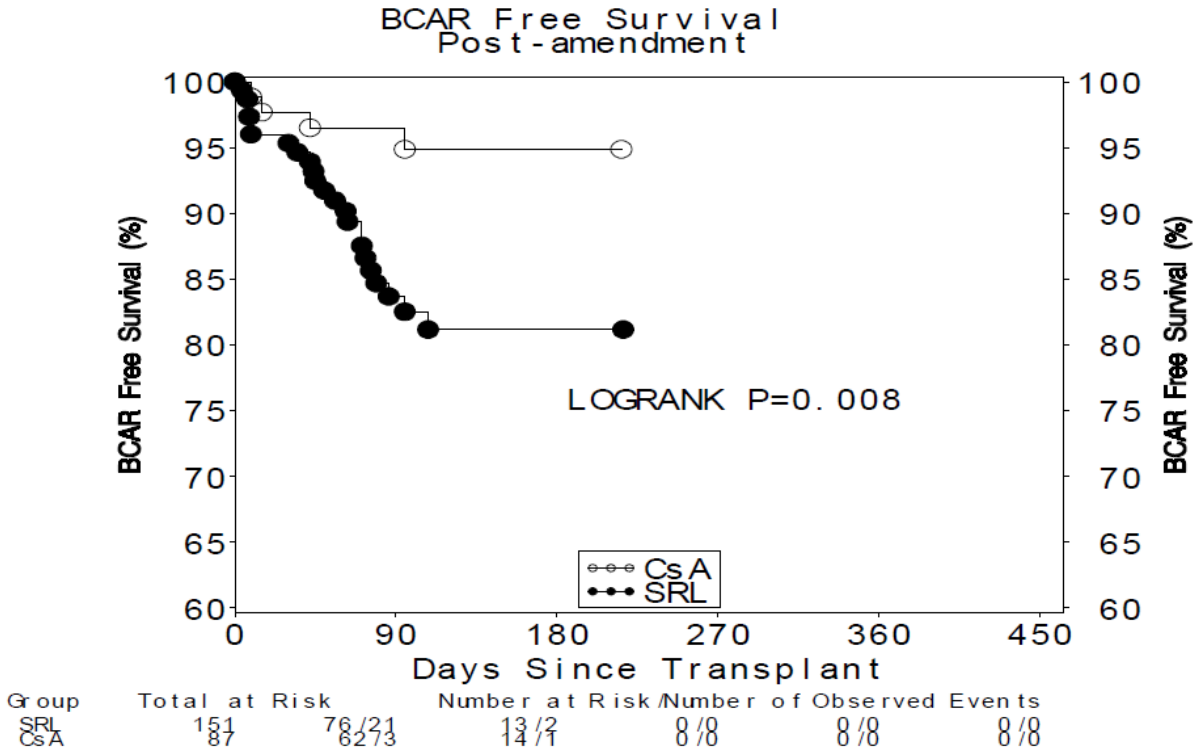
Figure 1. Time to First Biopsy-Confirmed Acute Rejection During the Study by Treatment Group



BCAR = biopsy-confirmed acute rejection; CsA = cyclosporine; ITT = intent-to-treat; SRL = sirolimus.

Figure 2 shows time to event analysis of rates of BCAR after the implementation of study amendment 2, which increased exposure to sirolimus by mandating a higher dosage until therapeutic trough levels were achieved. For the purposes of this analysis, only subjects randomly assigned on or after 01 January 2006 were included in the post-amendment population. Despite this change, rates of BCAR-free survival remained significantly greater in Group A (p=0.008). The rates of BCAR-free survival at 3 months were 84% in Group A and 96% in Group B. After amendment 2, there were 23 of 151 (15.2%) subjects with BCAR in Group A and 4 of 87 (4.6%) subjects with BCAR in Group B.

Figure 2. Time to First Biopsy-Confirmed Acute Rejection During the Study by Treatment Group, After Study Amendment 2



BCAR = biopsy-confirmed acute rejection; CsA = cyclosporine; SRL = sirolimus.

Histologic Grade of Severity of BCAR: Table 8 presents the number and percentage of subjects in the ITT population with first BCAR by treatment group and severity. Higher acute rejection rates of all grades of severity (mild, moderate, and severe) were observed in treatment Group A, although the majority of events were mild in both groups. Moderate or severe acute rejection was observed in 5.4% and 1.2% of subjects in Groups A and B, respectively. This difference in severity of acute rejections was statistically significantly different ($p < 0.001$). However, the rate of graft loss at the time of study termination (11 subjects (3.5%) in Group A and 5 subjects (3.1%) in Group B) was similar between groups.

Table 8. Number (%) of Subjects by Severity of Biopsy-Confirmed Acute Rejection: ITT Population

Severity of BCAR	SRL Regimen (n=314)	CsA Regimen (n=161)	p-Value[a]
No rejection	253 (80.6)	153 (95.0)	<0.001***
Mild	44 (14.0)	6 (3.7)	
Moderate	16 (5.1)	2 (1.2)	
Severe	1 (0.3)	0	

BCAR = biopsy-confirmed acute rejection; CsA = cyclosporine; ITT = intent-to-treat; n = number of subjects in each treatment group; SRL = sirolimus.

a. Cochran-Mantel-Haenszel row mean score assigning 0, 1, 2, and 3 to no rejection, mild, moderate, and severe, respectively. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Mean On-Therapy Calculated Nankivell Glomerular Filtration Rate: The mean on-therapy calculated Nankivell GFR was planned for evaluation at 24, 52, 104, 156, and 208 weeks. The results available through the time of study termination are presented in Table 9. At all visits, mean Nankivell GFR was numerically higher among subjects in Group A. At Week 4, this difference was statistically significant (p=0.029).

Table 9. Observed Mean Calculated Nankivell Glomerular Filtration Rate (mL/min ±SD) by Treatment Group and Post-Transplant Visit: Safety Population

Visit	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Overall p-Value[a]
Week 4	68.23±21.32 (165)[b]	62.64±16.06 (92)	0.029*
Week 8	66.95±17.81 (144)	63.73±13.64 (85)	0.152
Week 12	66.63±18.18 (123)	66.27±14.25 (74)	0.886
Week 24	70.00±19.80 (68)	65.50±13.89 (41)	0.205
Week 52	72.39±12.28 (3)	62.56±8.55 (2)	0.406

CsA = cyclosporine; n = number of subjects in each treatment group; SD = standard deviation; SRL = sirolimus.

a. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

b. Number of observations used to calculate the mean.

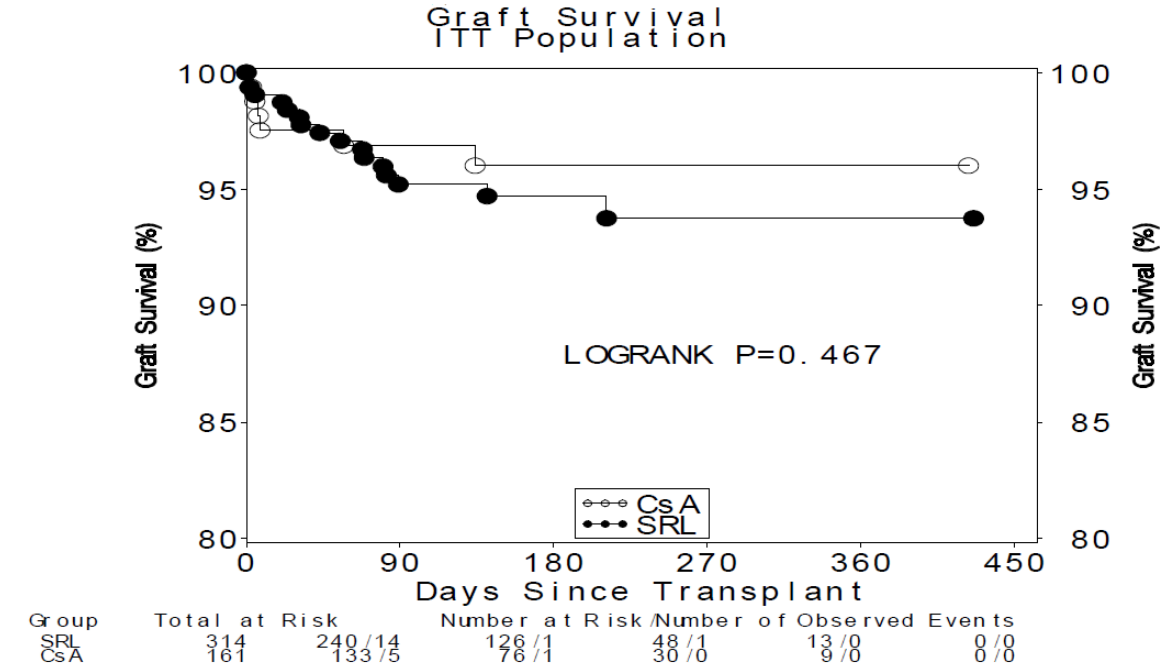
Since the study was terminated prematurely, the analyses of the other efficacy endpoints, including mean Nankivell GFR (ITT) at 24, 104, 156, and 208 weeks, slopes of 1/creatinine vs time at 24, 52, 104, 156, and 208 weeks, slopes of calculated Nankivell GFR vs time at 24, 52, 104, 156, and 208 weeks, mean GFR measured by radionuclide or comparable methodology at 24, 52, and 104 weeks at participating centers, progression of CAN at 52 weeks at participating centers, and QoL outcomes at 24, 52, and 104 weeks, were not performed because the data were not available.

Safety Results:

Graft Survival: The time to graft loss is presented in Figure 3 by treatment group. The Kaplan-Meier estimates of graft survival over time showed there was no significant difference between the 2 treatment groups (p=0.467). At Month 6, graft survival was 95% in

Group A and 96% in Group B. At Month 12, graft survival was 94% in Group A and 96% in Group B.

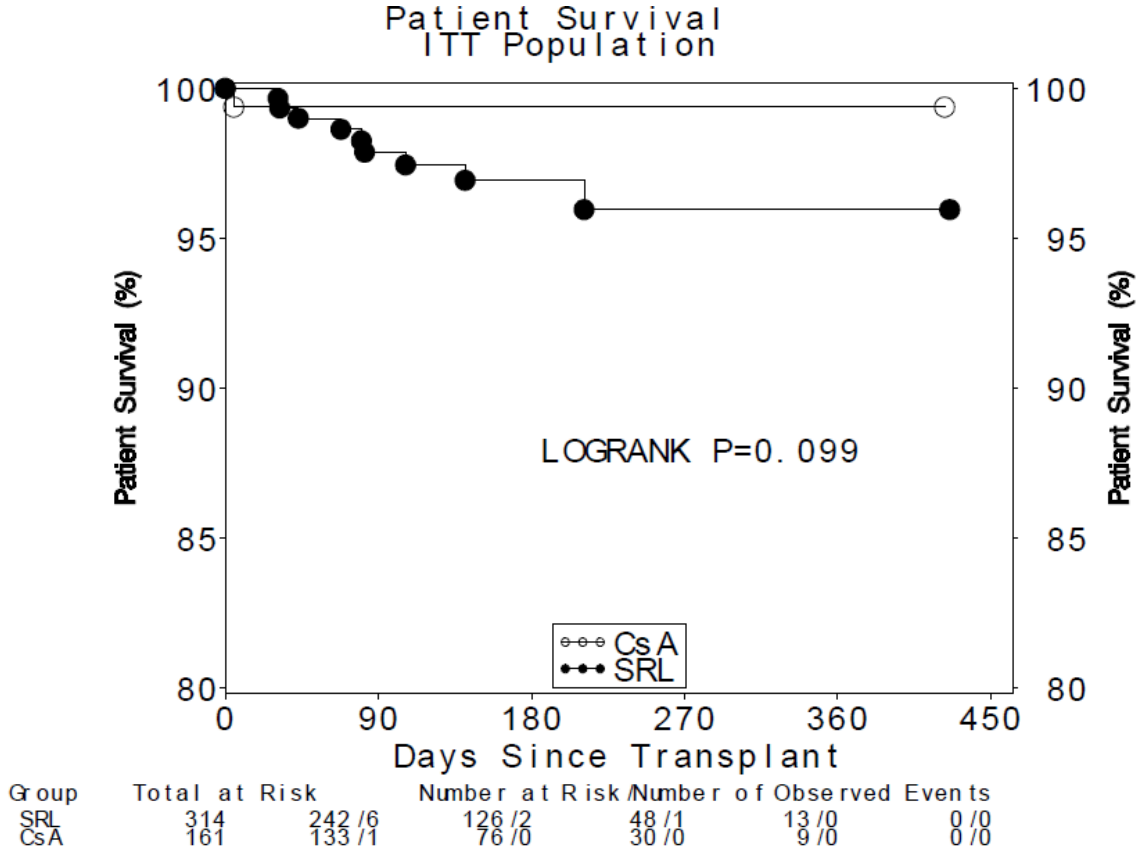
Figure 3. Time to Graft Loss During the Study by Treatment Group



CsA = cyclosporine; ITT = intent-to-treat; SRL = sirolimus.

Subject Survival: A time to event analysis of subject survival over the course of the study is presented in Figure 4 for each treatment group. Although subject survival over time was numerically lower in Group A than in Group B, the difference was not statistically significant (p=0.099).

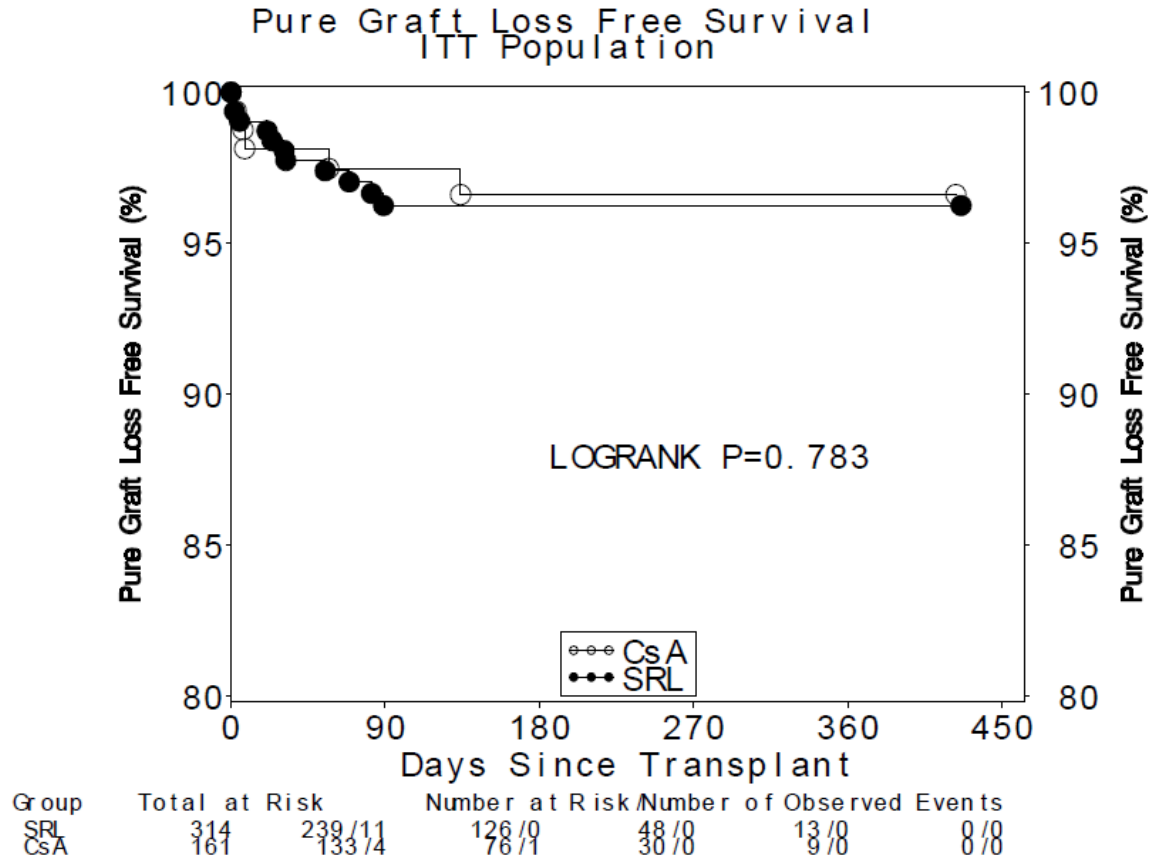
Figure 4. Time to Death During the Study by Treatment Group



CsA = cyclosporine; ITT = intent-to-treat; SRL = sirolimus.

Graft Survival (Death Censored): A time to event analysis of death-censored graft survival is presented in Figure 5. Although more subjects lost their grafts in Group A (11/314, 3.5%) than in Group B (5/161, 3.1%), the difference was not statistically significant.

Figure 5. Time to Event Analysis of Death - Censored Graft Survival



CsA = cyclosporine; ITT = intent-to-treat; SRL = sirolimus.

Mean Systolic and Diastolic Blood Pressures: Table 10 shows the observed mean values for sitting systolic BP for all subjects in both treatment groups at those visits performed during study therapy. At Week 4, subjects in Group A had numerically higher mean systolic BP values; at Weeks 8 through 52, mean systolic BP values were higher for subjects in Group B. The differences between groups were not statistically significant.

Table 10. Observed Mean Values (± SD) for Sitting Systolic Blood Pressure (mm Hg) by Treatment Group and Post-Transplant Visit: Safety Population During Therapy

Visit	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Overall p-Value[a]
Week 4	137.89±18.64 (225)[b]	136.98±18.72 (127)	0.661
Week 8	134.95±17.27 (194)	135.33±16.09 (119)	0.847
Week 12	131.09±14.85 (166)	133.38±14.82 (104)	0.219
Week 24	126.02±13.17 (94)	130.39±14.88 (57)	0.062
Week 52	120.33±11.69 (6)	132.00± 22.80 (5)	0.300

CsA = cyclosporine; n = number of subjects in each treatment group; SD = standard deviation; SRL = sirolimus.
a. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.
b. Number of observations used to calculate the mean.

Table 11 shows the observed mean values for sitting diastolic BP for all subjects in both treatment groups at those visits performed during study therapy. At all visits, subjects in Group B had numerically higher mean diastolic BP values. The differences between groups were statistically significant at Week 12 and Week 24 (p=0.031 and p=0.030, respectively).

Table 11. Observed Mean Values (± SD) for Sitting Diastolic Blood Pressure (mm Hg) by Treatment Group and Post-Transplant Visit: Safety Population During Therapy

Visit	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Overall p-Value[a]
Week 4	80.76±11.37 (225)[b]	82.78±13.76 (127)	0.139
Week 8	80.88±10.05 (194)	81.74±11.65 (119)	0.488
Week 12	78.23±9.71 (166)	81.00±11.00 (104)	0.031*
Week 24	75.93±9.13 (94)	79.37±9.74 (57)	0.030*
Week 52	73.83±8.73 (6)	79.00±20.74 (5)	0.590

CsA = cyclosporine; n = number of subjects in each treatment group; SD = standard deviation; SRL = sirolimus.
a. Statistical significance at the 0.05 is denoted by *.
b. Number of observations used to calculate the mean.

Incidence of Infection: Table 12 presents the number and percentage of subjects who reported TEAEs related to infections with an incidence of ≥2% in either treatment group. Treatment-emergent pneumonia was reported only in Group A, and at a rate (2.9%) that differed significantly from 0 (p=0.031). Additionally, the most common infection-related TEAEs overall were infection (18.1% in Group A and 24.8% in Group B) and urinary tract infection (21.3% in Group A and 21.1% in Group B).

Table 12. Number (%) of Subjects With Infections Reported as TEAEs With an Incidence ≥2%, by Treatment Group, Body System, and Preferred Term: Safety Population

COSTART Body System[a] Adverse Event Preferred Term	Sex	Overall p-Value[b]	Group A SRL Regimen F (n=95) M (n=215) (n=310)	Group B CsA Regimen F (n=45) M (n=116) (n=161)	Total F (n=140) M (n=331) (N=471)
Any AEs		0.174	156 (50.3)	92 (57.1)	248 (52.7)
Body as a whole					
Infection		0.092	56 (18.1)	40 (24.8)	96 (20.4)
Sepsis		0.154	12 (3.9)	2 (1.2)	14 (3.0)
Digestive system					
Diarrhea		0.274	7 (2.3)	1 (0.6)	8 (1.7)
Oral moniliasis		0.522	6 (1.9)	5 (3.1)	11 (2.3)
Respiratory system					
Pneumonia		0.031*	9 (2.9)	0	9 (1.9)
Upper respiratory infection		0.646	15 (4.8)	6 (3.7)	21 (4.5)
Skin and appendages					
Fungal dermatitis		0.129	3 (1.0)	5 (3.1)	8 (1.7)
Herpes simplex		1.000	15 (4.8)	7 (4.3)	22 (4.7)
Urogenital system					
Pyelonephritis		1.000	7 (2.3)	3 (1.9)	10 (2.1)
Urinary tract infection		1.000	66 (21.3)	34 (21.1)	100 (21.2)
Vaginitis[c]	F	1.000	2 (2.1)	0	2 (1.4)

AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; CsA = cyclosporine; F = female; M = male; N = total number of subjects; n = number of subjects in each treatment group; SRL = sirolimus; TEAEs = treatment-emergent adverse events.

a. A subject could have reported ≥2 different AEs in the same body system.
b. Overall p-value: Fisher exact test p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.
c. Sex-related event; the percentage is calculated using as the denominator the number of female subjects in Group A (95) or Group B (45).

Incidence of Malignancy: Table 13 presents the number and percentage of subjects who reported treatment-emergent malignancies. Treatment-emergent malignancies were reported for 3 subjects (0.6%). The treatment difference in the rate of these reported events was not statistically significant.

Table 13. Number (%) of Subjects With Malignancies Reported as TEAEs by Treatment Group, Body System, and Preferred Term: Safety Population

COSTART Body System[a] Adverse Event Preferred Term	Overall p-Value[b]	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Total (N=471)
Any AEs	0.270	1 (0.3)	2 (1.2)	3 (0.6)
Cardiovascular system				
Vascular anomaly	0.342	0	1 (0.6)	1 (0.2)
Skin and appendages				
Skin carcinoma	0.342	0	1 (0.6)	1 (0.2)
Urogenital system				
Bladder carcinoma	1.000	1 (0.3)	0	1 (0.2)

AE = adverse event; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; CsA = cyclosporine; N = total number of subjects; n = number of subjects in each treatment group; SRL = sirolimus; TEAEs = treatment-emergent adverse events.

a. A subject could have reported ≥2 different AEs in the same body system.
b. Overall p-value: Fisher exact test p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Incidence of Delayed Graft Function: Table 14 presents the number and percentage of subjects who experienced DGF by treatment group. The incidence of DGF was 20.4% in Group A and 22.4% in Group B; this difference was not statistically significant.

Table 14. Delayed Graft Function: ITT Population

Treatment	Number of Subjects[a]	Number (%) of Subjects With DGF	Difference (SE) (SRL - CsA)	95% CI (Asymptotic)	p-Value (Fisher Exact Test, 2-Sided)[b]
SRL (Group A)	313	64 (20.4)	-1.9 (4.0)	(-9.7, 5.9)	0.636
CsA (Group B)	161	36 (22.4)			

CI = confidence interval; CsA = cyclosporine; DGF = delayed graft function; ITT = intent-to-treat; SE = standard error; SRL = sirolimus.

a. Excluded was 1 SRL subject (whose DGF status could not be determined because the subject withdrew on Study Day 1).
b. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

The rates of DGF among deceased and living donor allograft recipients are presented in Table 15 and Table 16, respectively. Within each of these donor categories, the rate of DGF was numerically similar between treatment groups and the difference was not statistically significant.

Table 15. Rate of Delayed Graft Function, Deceased Donor: ITT Population

Treatment	Number of Subjects[a]	Number (%) of Subjects With DGF	Difference (SE) (SRL - CsA)	95% CI (Asymptotic)	p-Value (Fisher Exact Test, 2-Sided)[b]
SRL (Group A)	186	57 (30.6)	-1.6 (5.9)	(-13.2, 10.0)	0.786
CsA (Group B)	93	30 (32.3)			

CI = confidence interval; CsA = cyclosporine; DGF = delayed graft function; ITT = intent-to-treat; SE = standard error; SRL = sirolimus.

a. Excluded was 1 sirolimus subject (whose DGF status could not be determined because the subject withdrew on Study Day 1.

b. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Table 16. Rate of Delayed Graft Function, Living Donor: ITT Population

Treatment	Number of Subjects[a]	Number (%) of Subjects With DGF	Difference (SE) (SRL - CsA)	95% CI (Asymptotic)	p-Value (Fisher Exact Test, 2-Sided)[b]
SRL (Group A)	127	7 (5.5)	-3.3 (4.0)	(-11.1, 4.5)	0.382
CsA (Group B)	68	6 (8.8)			

CI = confidence interval; CsA = cyclosporine; DGF = delayed graft function; ITT = intent-to-treat; SE = standard error; SRL = sirolimus.

a. Excluded was 1 sirolimus subject whose DGF status could not be determined because the subject withdrew on Study Day 1.

b. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Table 17 presents the rate of recovery among those subjects in each treatment group who experienced DGF. The rate of recovery from DGF was higher in the sirolimus treatment group, although the difference was not statistically significant.

Table 17. Rate of Recovery From Delayed Graft Function: All Subjects With Delayed Graft Function

Treatment	Number of Subjects[a]	Number (%) of Subjects With DGF Who Recovered	Difference (SE) (SRL - CsA)	95% CI (Asymptotic)	p-Value (Fisher Exact Test, 2-Sided)[b]
SRL (Group A)	61	58 (95.1)	9.0 (6.4)	(-3.6, 21.5)	0.143
CsA (Group B)	36	31 (86.1)			

CI = confidence interval; CsA = cyclosporine; DGF = delayed graft function; SE = standard error; SRL = sirolimus.

a. Excluded were 3 sirolimus subjects whose recovery from DGF could not be determined because the subjects withdrew on or before Study Day 60. If all 3 subjects were scored as not recovering, the rate in the sirolimus group was 90.6%.

b. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Table 18 presents the distribution of duration of DGF by treatment group. Among subjects who experienced DGF, the mean and median times to recovery were slightly longer in Group A when compared with Group B; however, the median difference was not statistically significant.

Table 18. Duration of Delayed Graft Function: ITT Population

Duration of DGF (Days)	Group A SRL Regimen[a] (n=58)	Group B CsA Regimen (n=31)	p-Value[b] (Rank Sum) (SRL - CsA)
Mean (SE)	9.9 (9.1)	8.5 (7.1)	0.564
Minimum	1.0	1.0	
Maximum	43.0	29.0	
P 25	4.0	3.0	
P 50	7.5	7.0	
P 75	11.0	11.0	

CsA = cyclosporine; DGF = delayed graft function; ITT = intent-to-treat; n = number of subjects in each treatment group; P = percentile; SE = standard error; SRL = sirolimus.

a. Excluded were 3 sirolimus subjects whose recovery from DGF could not be determined because the subjects withdrew on or before Study Day 60. All subjects in this analysis recovered; accordingly, there were no censored data.

b. Rank sum p-value. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Incidence of Wound Healing Complications: Table 19 presents the number and percentage of subjects in both treatment groups who experienced wound healing complications, by degree of severity. A greater percentage of subjects in Group A experienced both Grade 1 (required surgery) and Grade 2 (did not require surgery) wound complications. When compared with Group A, a greater percentage of subjects in Group B had surgical wounds that healed without complications; the differences were statistically significant (p=0.033).

Table 19. Severity of Wound Healing Complications: ITT Population

Wound Healing Complications	Group A SRL Regimen[a] (n=302)	Group B CsA Regimen[a] (n=159)	p-Value[b]
Severity			
Healed	256 (84.8)	146 (91.8)	0.033*
Grade 2 (no surgery)	33 (10.9)	10 (6.3)	
Grade 1 (required surgery)	13 (4.3)	3 (1.9)	

CsA = cyclosporine; ITT = intent-to-treat; n = number of subjects in each treatment group; SRL = sirolimus.

a. Excluded were 14 subjects (SRL=12; CsA=2) who were missing wound healing assessments at both Weeks 4 and 12.

b. Cochran-Mantel-Haenszel row mean score assigning 0, 1, and 2 to healed, Grade 2, and Grade 1, respectively. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Incidence of Post-Transplant Diabetes Mellitus: The analysis of the incidence of diabetes mellitus, defined as 30 consecutive days of new insulin use, was not performed. However, the Investigator-reported rate of treatment-emergent diabetes mellitus was similar for Groups A and B (5.2% and 5.0%, respectively; Table 25). In addition, rates of insulin use were similar for both groups. The percentage of subjects receiving insulin before and after transplantation is shown in Table 20. Before transplantation, insulin was received by 39 (12.6%) subjects in Group A and by 17 (10.6%) subjects in Group B. After transplantation, the percentage of subjects receiving insulin while on therapy increased and was of similar magnitude in both treatment groups (75 [24.2%] subjects in Group A and 40 [24.8%] subjects in Group B). Among those who received any dose of insulin while on

therapy, rates of new insulin use, ie, those who had not taken insulin before entering the study, were 18.4% in Group A and 17.4% in Group B.

Table 20. Number (%) of Subjects Receiving Insulin Before and After Transplantation by Treatment Group: Safety Population

ATC Classification[a]	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Total (N=471)	p-Value (Fisher Exact Test, 2-Sided)[b]
Before transplantation				
Total insulins	39 (12.6)	17 (10.6)	56 (11.9)	0.552
After transplantation (on-therapy)				
Total insulins	75 (24.2)	40 (24.8)	115 (24.4)	0.910

ATC = Anatomical Therapeutic Chemical; CsA = cyclosporine; N = total number of subjects; n = number of subjects in each treatment group; SRL = sirolimus.

a. Classification totals were not necessarily the sum of the individual non-study medications, since a subject may have reported ≥2 different non-study medications in the same classification.
b. Overall p-value: Fisher exact test, p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Cumulative Use of Lipid-Lowering Agents: Table 21 presents the number and percentage of subjects in both treatment groups who received any lipid-lowering agent during the study. A total of 288 (61.1%) subjects received any lipid lowering agent during the study. These agents were prescribed for 201 subjects (64.8%) in Group A and for 87 subjects (54.0%) in Group B, a difference that was statistically significant (p=0.028). A majority of subjects in both treatment groups received hydroxymethyl glutaryl coenzyme A reductase inhibitors (Group A: 192 subjects [61.9%]; Group B: 80 subjects [49.7%]); this difference was statistically significant (p=0.014) and was expected, given the known effect of sirolimus on serum lipid levels.

Table 21. Number (%) of Subjects Concomitantly Receiving Lipid-Lowering Agents by Treatment Group: Safety Population

ATC Classification[a]	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Total (N=471)	p-Value (Fisher Exact Test, 2-Sided)[b]
Total lipid-lowering agents	201 (64.8)	87 (54.0)	288 (61.1)	0.028*
HMG-CoA reductase inhibitors	192 (61.9)	80 (49.7)	272 (57.7)	0.014*
Fibrates	26 (8.4)	6 (3.7)	32 (6.8)	0.081
Other cholesterol and triglyceride reducers	24 (7.7)	9 (5.6)	33 (7.0)	0.450
Cholesterol and triglyceride reducers	1 (0.3)	0	1 (0.2)	1.000
Dihydropyridine derivative	1 (0.3)	0	1 (0.2)	1.000
Other antithrombotic agents	1 (0.3)	0	1 (0.2)	1.000
Other therapeutic products	1 (0.3)	0	1 (0.2)	1.000
Nicotinic acid and derivatives	0	1 (0.6)	1 (0.2)	0.342

ATC = Anatomical Therapeutic Chemical; CsA = cyclosporine; HMG-CoA = hydroxymethyl glutaryl coenzyme A; N = total number of subjects; n = number of subjects in each treatment group; SRL = sirolimus.

a. Classification totals are not necessarily the sum of the individual non-study medications, since a subject may have reported ≥2 different non-study medications in the same classification.

b. Overall p-value: Fisher exact test, p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Cumulative Use of Antihypertensive Medications: Table 22 presents the number and percentage of subjects in both treatment groups who received any antihypertensive medication during the study. In Groups A and B, 273 and 150 subjects (88.1% and 93.2%, respectively) received ≥1 antihypertensive medication during the study; the overall difference was not significant (p=0.107). In both treatment groups, a majority of subjects most commonly received plain selective beta-blocking agents, dihydropyridine derivatives, or other calcium channel blockers, none of these differences were significant.

Table 22. Number (%) of Subjects Concomitantly Receiving Antihypertensive Medications by Treatment Group, Reported by ≥10% of Total Subjects: Safety Population

ATC Classification[a]	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Total (N=471)	p-Value (Fisher Exact Test, 2-Sided)[b]
Total antihypertensive medication	273 (88.1)	150 (93.2)	423 (89.8)	0.107
Beta-blocking agent, plain, selective	187 (60.3)	92 (57.1)	279 (59.2)	0.553
Dihydropyridine derivatives	127 (41.0)	74 (46.0)	201 (42.7)	0.326
Calcium channel blockers	100 (32.3)	55 (34.2)	155 (32.9)	0.681
Converting enzyme blockers	85 (27.4)	42 (26.1)	127 (27.0)	0.827
Alpha-adrenoceptor-blocking agents	64 (20.6)	18 (11.2)	82 (17.4)	0.010*
Imidazoline receptor agonists	48 (15.5)	17 (10.6)	65 (13.8)	0.160
Other agents acting on the renin-angiotensin system	27 (11.9)	17 (10.6)	54 (11.5)	0.761

ATC = Anatomical Therapeutic Chemical; CsA = cyclosporine; N = total number of subjects; n = number of subjects in each treatment group; SRL = sirolimus.

a. Classification totals are not necessarily the sum of the individual non-study medications, since a subject may have reported ≥2 different non-study medications in the same classification.
b. Overall p-value: Fisher exact test, p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Use of Recombinant Erythropoietic Agents: The percentage of subjects receiving recombinant erythropoietic agents before and after transplantation is shown in Table 23. After transplantation, the percentage of subjects receiving erythropoietic agents during the study decreased in both treatment groups (133 [42.9%] subjects in Group A and 55 [34.2%] subjects in Group B), but to a statistically significant (p <0.001) greater extent in Group B.

Table 23. Number (%) of Subjects Receiving Erythropoietic Agents Before and After Transplantation by Treatment Group: Safety Population

ATC Classification[a]	Group A SRL Regimen (n=310)	Group B CsA Regimen (n=161)	Total (N=471)	p-Value (Fisher Exact Test, 2-Sided)[b]
Before transplantation				
Erythropoietic agents	191 (61.6)	98 (60.9)	289 (61.4)	0.921
After transplantation				
Erythropoietic agents	102 (32.9)	26 (16.1)	128 (27.2)	<0.001***

ATC = Anatomical Therapeutic Chemical; CsA = cyclosporine; N = total number of subjects; n = number of subjects in each treatment group; SRL = sirolimus.

a. Classification totals are not necessarily the sum of the individual non-study medications, since a subject may have reported ≥2 different non-study medications in the same classification.
b. Overall p-value: Fisher exact test, p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Serious Adverse Events: Throughout the study, serious adverse events (SAEs) were reported significantly more often in Group A than in Group B (54.8% vs 41.0%, p = 0.005). The most commonly occurring SAEs during this study were creatinine increased, diarrhea, healing abnormal, kidney tubular necrosis, and transplant rejection. Those SAEs reported significantly more frequently in Group A vs Group B were transplant rejection (18.7% vs

4.3%; p <0.001) and diarrhea (7.1% vs 1.2%; p=0.007). Number (%) of subjects reporting SAEs is presented in Table 24 which summarizes all SAEs that occurred during the study.

Table 24. Number (%) of Subjects Reporting Adverse Events: Serious Adverse Events

COSTART Body System[a] Adverse Event, Preferred Term	Sex	Overall p-Value[b]	Group A SRL Regimen M (n=215) (n=310)	Group B CsA Regimen M (n=116) (n=161)	Total M (n=331) (N=471)
Any adverse event		0.005**	170 (54.8)	66 (41.0)	236 (50.1)
Body as a whole		<0.001***	98 (31.6)	22 (13.7)	120 (25.5)
Abdominal pain		0.346	9 (2.9)	2 (1.2)	11 (2.3)
Abscess		1.000	1 (0.3)	1 (0.6)	2 (0.4)
Accidental injury		1.000	1 (0.3)	0	1 (0.2)
Accidental overdose		1.000	1 (0.3)	0	1 (0.2)
Anaphylactoid reaction		0.549	2 (0.6)	0	2 (0.4)
Asthenia		1.000	1 (0.3)	0	1 (0.2)
Back pain		0.342	0	1 (0.6)	1 (0.2)
Cellulitis		0.342	0	1 (0.6)	1 (0.2)
Chest pain		0.342	0	1 (0.6)	1 (0.2)
Cyst		1.000	1 (0.3)	0	1 (0.2)
Death		1.000	1 (0.3)	0	1 (0.2)
Drug level increased		1.000	3 (1.0)	1 (0.6)	4 (0.8)
Fever		0.406	8 (2.6)	7 (4.3)	15 (3.2)
Headache		0.554	3 (1.0)	0	3 (0.6)
Hernia		1.000	3 (1.0)	1 (0.6)	4 (0.8)
Immune system disorder		0.549	2 (0.6)	0	2 (0.4)
Infection		1.000	1 (0.3)	0	1 (0.2)
Lymphocele		0.474	15 (4.8)	5 (3.1)	20 (4.2)
Overdose		0.171	5 (1.6)	0	5 (1.1)
Pain		1.000	1 (0.3)	0	1 (0.2)
Peritonitis		0.549	2 (0.6)	0	2 (0.4)
Retroperitoneal hemorrhage		1.000	1 (0.3)	0	1 (0.2)
Sepsis		0.549	2 (0.6)	0	2 (0.4)
Transplant rejection		<0.001***	58 (18.7)	7 (4.3)	65 (13.8)
Cardiovascular system		0.126	40 (12.9)	13 (8.1)	53 (11.3)
Arterial anomaly		0.431	6 (1.9)	1 (0.6)	7 (1.5)
Arterial thrombosis		1.000	1 (0.3)	0	1 (0.2)
Atrial fibrillation		0.270	1 (0.3)	2 (1.2)	3 (0.6)
Atrial flutter		0.549	2 (0.6)	0	2 (0.4)
Cardiovascular disorder		1.000	1 (0.3)	0	1 (0.2)
Cerebral ischemia		0.342	0	1 (0.6)	1 (0.2)
Cerebrovascular accident		0.342	0	1 (0.6)	1 (0.2)
Deep vein thrombosis		0.056	8 (2.6)	0	8 (1.7)
Heart arrest		0.549	2 (0.6)	0	2 (0.4)
Heart failure		1.000	1 (0.3)	1 (0.6)	2 (0.4)
Hemorrhage		0.695	4 (1.3)	3 (1.9)	7 (1.5)
Hypertension		1.000	1 (0.3)	1 (0.6)	2 (0.4)
Hypervolemia		1.000	1 (0.3)	0	1 (0.2)
Hypovolemia		1.000	1 (0.3)	0	1 (0.2)
Infarct		0.549	2 (0.6)	0	2 (0.4)
Left heart failure		1.000	1 (0.3)	0	1 (0.2)
Migraine		0.342	0	1 (0.6)	1 (0.2)
Myocardial infarct		0.304	4 (1.3)	0	4 (0.8)
Myocardial ischemia		0.549	2 (0.6)	0	2 (0.4)
Occlusion		1.000	1 (0.3)	0	1 (0.2)
Peripheral vascular disorder		1.000	1 (0.3)	0	1 (0.2)
Phlebitis		1.000	1 (0.3)	0	1 (0.2)
Pulmonary embolus		0.342	0	1 (0.6)	1 (0.2)

Table 24. Number (%) of Subjects Reporting Adverse Events: Serious Adverse Events

COSTART Body System[a] Adverse Event, Preferred Term	Sex	Overall p-Value[b]	Group A SRL Regimen M (n=215) (n=310)	Group B CsA Regimen M (n=116) (n=161)	Total M (n=331) (N=471)
Shock		0.549	2 (0.6)	0	2 (0.4)
Supraventricular tachycardia		1.000	1 (0.3)	0	1 (0.2)
Syncope		1.000	2 (0.6)	1 (0.6)	3 (0.6)
Thrombophlebitis		1.000	1 (0.3)	0	1 (0.2)
Thrombosis		1.000	1 (0.3)	0	1 (0.2)
Vascular thrombosis of transplanted organ		1.000	2 (0.6)	1 (0.6)	3 (0.6)
Venous pressure increased		1.000	1 (0.3)	0	1 (0.2)
Digestive system		0.038*	39 (12.6)	10 (6.2)	49 (10.4)
Cholecystitis		0.549	2 (0.6)	0	2 (0.4)
Colitis		1.000	1 (0.3)	1 (0.6)	2 (0.4)
Diarrhea		0.007**	22 (7.1)	2 (1.2)	24 (5.1)
Dysphagia		0.549	2 (0.6)	0	2 (0.4)
Esophageal ulcer		1.000	1 (0.3)	0	1 (0.2)
Gastroenteritis		0.342	0	1 (0.6)	1 (0.2)
Gastrointestinal disorder		0.549	2 (0.6)	0	2 (0.4)
Gastrointestinal hemorrhage		0.549	2 (0.6)	0	2 (0.4)
Hematemesis		1.000	1 (0.3)	0	1 (0.2)
Hepatitis		1.000	1 (0.3)	0	1 (0.2)
Ileus		1.000	2 (0.6)	1 (0.6)	3 (0.6)
Intestinal obstruction		1.000	1 (0.3)	0	1 (0.2)
Intestinal perforation		1.000	1 (0.3)	0	1 (0.2)
Liver function tests abnormal		0.342	0	1 (0.6)	1 (0.2)
Melena		1.000	1 (0.3)	0	1 (0.2)
Nausea		1.000	1 (0.3)	0	1 (0.2)
Nausea and vomiting		1.000	1 (0.3)	0	1 (0.2)
Pancreatitis		0.342	0	1 (0.6)	1 (0.2)
Peptic ulcer		1.000	1 (0.3)	0	1 (0.2)
Peptic ulcer hemorrhage		0.342	0	1 (0.6)	1 (0.2)
Rectal disorder		1.000	1 (0.3)	0	1 (0.2)
Stomach ulcer		1.000	1 (0.3)	0	1 (0.2)
Vomiting		0.609	2 (0.6)	2 (1.2)	4 (0.8)
Endocrine system		0.270	1 (0.3)	2 (1.2)	3 (0.6)
Adrenal cortex insufficiency		1.000	1 (0.3)	0	1 (0.2)
Diabetes mellitus		0.342	0	1 (0.6)	1 (0.2)
Parathyroid disorder		0.342	0	1 (0.6)	1 (0.2)
Hemic and lymphatic system		0.176	24 (7.7)	7 (4.3)	31 (6.6)
Anemia		0.274	7 (2.3)	1 (0.6)	8 (1.7)
Coagulation disorder		1.000	1 (0.3)	0	1 (0.2)
International normalised ratio increased		1.000	1 (0.3)	0	1 (0.2)
Leukocytosis		0.116	0	2 (1.2)	2 (0.4)
Leukopenia		0.175	8 (2.6)	1 (0.6)	9 (1.9)
Neutropenia		0.270	1 (0.3)	2 (1.2)	3 (0.6)
Pancytopenia		0.549	2 (0.6)	0	2 (0.4)
Thrombocytopenia		1.000	3 (1.0)	1 (0.6)	4 (0.8)
Thrombotic thrombocytopenic purpura		1.000	3 (1.0)	1 (0.6)	4 (0.8)
Metabolic and nutritional		0.140	53 (17.1)	19 (11.8)	72 (15.3)

Table 24. Number (%) of Subjects Reporting Adverse Events: Serious Adverse Events

COSTART Body System[a] Adverse Event, Preferred Term	Sex	Overall p-Value[b]	Group A SRL Regimen M (n=215) (n=310)	Group B CsA Regimen M (n=116) (n=161)	Total M (n=331) (N=471)
Bun increased		0.549	2 (0.6)	0	2 (0.4)
Creatinine increased		0.606	29 (9.4)	12 (7.5)	41 (8.7)
Dehydration		0.118	1 (0.3)	3 (1.9)	4 (0.8)
Edema		1.000	1 (0.3)	0	1 (0.2)
Healing abnormal		0.136	16 (5.2)	3 (1.9)	19 (4.0)
Hypercalcemia		0.342	0	1 (0.6)	1 (0.2)
Hyperglycemia		0.554	3 (1.0)	0	3 (0.6)
Hyperkalemia		1.000	1 (0.3)	1 (0.6)	2 (0.4)
Hypoglycemia		1.000	1 (0.3)	0	1 (0.2)
Hypoglycemic reaction		1.000	1 (0.3)	0	1 (0.2)
Hypokalemia		0.549	2 (0.6)	0	2 (0.4)
Hyponatremia		0.116	0	2 (1.2)	2 (0.4)
Hypophosphatemia		0.549	2 (0.6)	0	2 (0.4)
Peripheral edema		0.554	3 (1.0)	0	3 (0.6)
SGPT increased		1.000	1 (0.3)	0	1 (0.2)
Nervous system		1.000	3 (1.0)	1 (0.6)	4 (0.8)
Confusion		1.000	1 (0.3)	0	1 (0.2)
Convulsion		0.342	0	1 (0.6)	1 (0.2)
Depression		1.000	1 (0.3)	0	1 (0.2)
Somnolence		1.000	1 (0.3)	0	1 (0.2)
Vertigo		1.000	1 (0.3)	0	1 (0.2)
Respiratory system		1.000	11 (3.5)	6 (3.7)	17 (3.6)
Cough increased		1.000	1 (0.3)	1 (0.6)	2 (0.4)
Dyspnea		0.609	2 (0.6)	2 (1.2)	4 (0.8)
Epistaxis		1.000	1 (0.3)	0	1 (0.2)
Lung disorder		0.549	2 (0.6)	0	2 (0.4)
Lung edema		0.609	2 (0.6)	2 (1.2)	4 (0.8)
Lung infiltration NOS		1.000	1 (0.3)	1 (0.6)	2 (0.4)
Pneumonitis		1.000	1 (0.3)	0	1 (0.2)
Pneumothorax		1.000	1 (0.3)	0	1 (0.2)
Pulmonary physical finding		1.000	1 (0.3)	0	1 (0.2)
Respiratory failure		0.342	0	1 (0.6)	1 (0.2)
Skin and appendages		0.116	0	2 (1.2)	2 (0.4)
Herpes zoster		0.342	0	1 (0.6)	1 (0.2)
Skin disorder		0.342	0	1 (0.6)	1 (0.2)
Urogenital system		1.000	44 (14.2)	22 (13.7)	66 (14.0)
Acute kidney failure		1.000	5 (1.6)	3 (1.9)	8 (1.7)
Albuminuria		1.000	1 (0.3)	0	1 (0.2)
Hematuria		1.000	1 (0.3)	0	1 (0.2)
Hydronephrosis		1.000	2 (0.6)	1 (0.6)	3 (0.6)
Hydroureter		1.000	1 (0.3)	1 (0.6)	2 (0.4)
Kidney failure		1.000	1 (0.3)	0	1 (0.2)
Kidney function abnormal		1.000	7 (2.3)	4 (2.5)	11 (2.3)
Kidney tubular disorder		1.000	1 (0.3)	0	1 (0.2)
Kidney tubular necrosis		0.113	19 (6.1)	4 (2.5)	23 (4.9)
Nephrocalcinosis		1.000	1 (0.3)	0	1 (0.2)
Oliguria		1.000	3 (1.0)	1 (0.6)	4 (0.8)
Prostatic disorder	M	1.000	1 (0.5)	1 (0.9)	2 (0.6)
Urinary incontinence		1.000	3 (1.0)	1 (0.6)	4 (0.8)
Urinary retention		0.116	0	2 (1.2)	2 (0.4)

Table 24. Number (%) of Subjects Reporting Adverse Events: Serious Adverse Events

COSTART Body System[a] Adverse Event, Preferred Term	Sex	Overall p-Value[b]	Group A SRL Regimen M (n=215) (n=310)	Group B CsA Regimen M (n=116) (n=161)	Total M (n=331) (N=471)
Urinary tract disorder		0.594	9 (2.9)	6 (3.7)	15 (3.2)
AEs assoc.w.misc. factors		1.000	11 (3.5)	5 (3.1)	16 (3.4)
Local reaction to procedure		0.783	11 (3.5)	4 (2.5)	15 (3.2)
Positive event		0.342	0	1 (0.6)	1 (0.2)

Sex - F, M, or blank indicates the calculation was based on subjects of either female only, male only, or both.
Overall p-value: Fisher's Exact test p-value (2-tail).
Statistical significance at the 0.05, 0.01, 0.001 levels is denoted by *, **, *** respectively.
AE = adverse event; assoc.w.misc = associated with miscellaneous; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; CsA = cyclosporine; F = female; M = male; N = total number of subjects; n = number of subjects in each treatment group; NOS = not otherwise specified; TEAEs = treatment-emergent adverse events; SRL = sirolimus.

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

Adverse Events (Excluding Infections and Malignancies): Table 25 shows the number and percentage of subjects who reported TEAEs with an incidence of ≥5% in either treatment group. A greater percentage of subjects in the sirolimus group (460, 97.7%) reported AEs: 460 subjects (97.7%) reported at least 1 AE during the study, 306 (98.7%) in the sirolimus group and 154 (95.7%) in the CsA group. The most common TEAEs occurring in ≥20% of subjects in either group included albuminuria, anemia, creatinine increased, diarrhea, hypercholesterolemia, hyperlipemia, hypertension, local reaction to procedure, and peripheral edema.

Table 25. Number (%) of Subjects Reporting TEAEs (Excluding Infections and Malignancies) With an Incidence ≥5%, by Treatment Group, Body System, and Preferred Term: Safety Population

COSTART Body System[a] Adverse Event, Preferred Term	Overall p-Value[b]	Group A SRL Regimen F (n=95) M (n=215) (n=310)	Group B CsA Regimen F (n=45) M (n=116) (n=161)	Total F (n=140) M (n=331) (N=471)
Any adverse event	0.052	306 (98.7)	154 (95.7)	460 (97.7)
Body as a whole				
Abdominal pain	0.881	36 (11.6)	20 (12.4)	56 (11.9)
Asthenia	0.497	13 (4.2)	9 (5.6)	22 (4.7)
Back pain	0.081	12 (3.9)	13 (8.1)	25 (5.3)
Chest pain	0.497	13 (4.2)	9 (5.6)	22 (4.7)
Fever	0.196	58 (18.7)	22 (13.7)	80 (17.0)
Headache	0.142	35 (11.3)	11 (6.8)	46 (9.8)
Lymphocele	0.106	29 (9.4)	8 (5.0)	37 (7.9)
Pain	0.066	42 (13.5)	12 (7.5)	54 (11.5)
Transplant rejection	<0.001***	59 (19.0)	9 (5.6)	68 (14.4)
Cardiovascular system				
Hemorrhage	0.654	14 (4.5)	9 (5.6)	23 (4.9)
Hypertension	0.665	84 (27.1)	47 (29.2)	131 (27.8)
Hypervolemia	0.189	19 (6.1)	5 (3.1)	24 (5.1)
Tachycardia	1.000	26 (8.4)	14 (8.7)	40 (8.5)
Digestive system				
Abdominal distension	0.409	20 (6.5)	7 (4.3)	27 (5.7)
Constipation	0.505	46 (14.8)	28 (17.4)	74 (15.7)
Diarrhea	<0.001***	95 (30.6)	21 (13.0)	116 (24.6)
Liver function tests abnormal	0.241	32 (10.3)	11 (6.8)	43 (9.1)
Nausea	0.787	46 (14.8)	26 (16.1)	72 (15.3)
Vomiting	0.112	34 (11.0)	26 (16.1)	60 (12.7)
Endocrine system				
Diabetes mellitus	1.000	16 (5.2)	8 (5.0)	24 (5.1)
Hemic and lymphatic system				
Anemia	0.060	134 (43.2)	55 (34.2)	189 (40.1)
Leukocytosis	0.086	6 (1.9)	8 (5.0)	14 (3.0)
Leukopenia	0.060	40 (12.9)	11 (6.8)	51 (10.8)
Thrombocytopenia	<0.001***	36 (11.6)	4 (2.5)	40 (8.5)
Metabolic and nutritional				
Creatinine increased	1.000	70 (22.6)	36 (22.4)	106 (22.5)
Edema	0.162	17 (5.5)	4 (2.5)	21 (4.5)
Healing abnormal	0.079	45 (14.5)	14 (8.7)	59 (12.5)
Hypercholesterolemia	0.432	80 (25.8)	36 (22.4)	116 (24.6)
Hyperglycemia	0.773	39 (12.6)	22 (13.7)	61 (13.0)
Hyperkalemia	0.289	22 (7.1)	16 (9.9)	38 (8.1)
Hyperlipemia	0.001**	137 (44.2)	46 (28.6)	183 (38.9)
Hyperuricemia	0.005**	8 (2.6)	14 (8.7)	22 (4.7)
Hypocalcemia	0.015*	25 (8.1)	4 (2.5)	29 (6.2)
Hypokalemia	0.004**	45 (14.5)	9 (5.6)	54 (11.5)
Hypomagnesemia	<0.001***	5 (1.6)	14 (8.7)	19 (4.0)
Hypophosphatemia	0.103	53 (17.1)	18 (11.2)	71 (15.1)
Lactate dehydrogenase increased	0.766	39 (12.6)	18 (11.2)	57 (12.1)
Peripheral edema	1.000	89 (28.7)	46 (28.6)	135 (28.7)
AST/SGOT increased	0.017*	19 (6.1)	2 (1.2)	21 (4.5)

Table 25. Number (%) of Subjects Reporting TEAEs (Excluding Infections and Malignancies) With an Incidence ≥5%, by Treatment Group, Body System, and Preferred Term: Safety Population

COSTART Body System[a] Adverse Event, Preferred Term	Overall p-Value[b]	Group A SRL Regimen F (n=95) M (n=215) (n=310)	Group B CsA Regimen F (n=45) M (n=116) (n=161)	Total F (n=140) M (n=331) (N=471)
ALT/SGPT increased	0.107	30 (9.7)	8 (5.0)	38 (8.1)
Weight gain	0.466	11 (3.5)	8 (5.0)	19 (4.0)
Musculoskeletal system				
Arthralgia	0.467	26 (8.4)	10 (6.2)	36 (7.6)
Osteoporosis	0.022*	5 (1.6)	9 (5.6)	14 (3.0)
Nervous system				
Insomnia	0.702	20 (6.5)	12 (7.5)	32 (6.8)
Paresthesia	0.119	8 (2.6)	9 (5.6)	17 (3.6)
Tremor	0.006**	7 (2.3)	13 (8.1)	20 (4.2)
Respiratory system				
Cough increased	0.335	24 (7.7)	8 (5.0)	32 (6.8)
Dyspnea	0.580	21 (6.8)	13 (8.1)	34 (7.2)
Skin and appendages				
Acne	0.053	52 (16.8)	16 (9.9)	68 (14.4)
Hirsutism	<0.001***	1 (0.3)	18 (11.2)	19 (4.0)
Special senses				
Abnormal vision	0.356	16 (5.2)	5 (3.1)	21 (4.5)
Urogenital system				
Albuminuria	0.005**	67 (21.6)	18 (11.2)	85 (18.0)
Dysuria	0.200	35 (11.3)	12 (7.5)	47 (10.0)
Hematuria	0.361	38 (12.3)	15 (9.3)	53 (11.3)
Kidney function abnormal	0.564	23 (7.4)	9 (5.6)	32 (6.8)
Kidney tubular necrosis	0.200	35 (11.3)	12 (7.5)	47 (10.0)
Urinary tract disorder	0.481	12 (3.9)	9 (5.6)	21 (4.5)
Adverse events associated with miscellaneous factors				
Local reaction to procedure	1.000	72 (23.2)	37 (23.0)	109 (23.1)

Non-SAEs and SAEs are not separated out.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; CsA = cyclosporine; F = female; M = male; N = total number of subjects; n = number of subjects in each treatment group; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; SAEs = serious adverse events; SRL = sirolimus; TEAEs = treatment-emergent adverse events.

a. A subject could have reported ≥2 different AEs in the same body system.
b. Overall p-value: Fisher exact test p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Discontinuations: The percentage of subjects who discontinued from the study because of a TEAE was significantly higher in Group A (48, 15.5%) than in Group B (11, 6.8%, p=0.008). The apparent discrepancy between the number of subjects in Group A reported as discontinuing because of an AE in Table 26 (48 subjects) and the number reported as discontinuing from the dosing phase of the study because of an AE (54 subjects, Table 6) was explained as follows: for 6 subjects for whom the reason for discontinuation was recorded as an AE on the conclusion of participation, there was no corresponding AE

marked with an outcome of discontinued dosing permanently on the AE. That is, for these 6 subjects, the specific AE, to which withdrawal from the study attributed was unknown.

In Group A, the TEAEs most frequently reported included healing abnormal (2.6%); leukopenia (1.6%); and drug level increased, kidney tubular necrosis, and urinary tract disorder (each 1.0%). In Group B, the TEAEs most frequently reported included drug level increased (1.2%) and hirsutism (1.9%). Hirsutism (0% Group A vs 1.9% Group B) was the only statistically significant (p=0.039) TEAE leading to discontinuation.

Table 26. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Study: Discontinued Study Treatment Permanently (AE, Inf, Mal)

Body System[a] Adverse Event	Overall p-Value	Treatment		
		SRL n=310	CSA n=161	Total N=471
Any adverse event	0.008**	48 (15.5)	11 (6.8)	59 (12.5)
Body as a whole	1.000	3 (1.0)	2 (1.2)	5 (1.1)
Drug level increased	1.000	1 (0.3)	0	1 (0.2)
Lymphocele	1.000	1 (0.3)	0	1 (0.2)
Overdose	0.342	0	1 (0.6)	1 (0.2)
Pain	0.342	0	1 (0.6)	1 (0.2)
Retroperitoneal hemorrhage	1.000	1 (0.3)	0	1 (0.2)
Cardiovascular system	1.000	4 (1.3)	2 (1.2)	6 (1.3)
Arterial thrombosis	1.000	1 (0.3)	0	1 (0.2)
Deep vein thrombosis	1.000	1 (0.3)	0	1 (0.2)
Hemorrhage	0.342	0	1 (0.6)	1 (0.2)
Peripheral vascular disorder	1.000	1 (0.3)	0	1 (0.2)
Vascular thrombosis of transplanted organ	1.000	1 (0.3)	1 (0.6)	2 (0.4)
Digestive system	1.000	3 (1.0)	2 (1.2)	5 (1.1)
Diarrhea	0.549	2 (0.6)	0	2 (0.4)
Gum hyperplasia	0.342	0	1 (0.6)	1 (0.2)
Hepatitis	1.000	1 (0.3)	0	1 (0.2)
Liver function tests abnormal	0.342	0	1 (0.6)	1 (0.2)
Hemic and lymphatic system	0.107	10 (3.2)	1 (0.6)	11 (2.3)
Anemia	1.000	1 (0.3)	0	1 (0.2)
Leukopenia	0.669	5 (1.6)	1 (0.6)	6 (1.3)
Pancytopenia	0.549	2 (0.6)	0	2 (0.4)
Thrombocytopenia	1.000	1 (0.3)	0	1 (0.2)
Thrombotic thrombocytopenic purpura	1.000	1 (0.3)	0	1 (0.2)
Metabolic and nutritional	0.066	11 (3.5)	1 (0.6)	12 (2.5)
Creatinine increased	0.342	0	1 (0.6)	1 (0.2)
Healing abnormal	0.056	8 (2.6)	0	8 (1.7)
Hyperlipemia	1.000	1 (0.3)	0	1 (0.2)
Hypokalemia	1.000	1 (0.3)	0	1 (0.2)
Peripheral edema	1.000	1 (0.3)	0	1 (0.2)
Musculoskeletal system	1.000	1 (0.3)	0	1 (0.2)
Arthralgia	1.000	1 (0.3)	0	1 (0.2)
Nervous system	1.000	1 (0.3)	1 (0.6)	2 (0.4)
Depression	1.000	1 (0.3)	0	1 (0.2)
Neuropathy	0.342	0	1 (0.6)	1 (0.2)
Respiratory system	0.554	3 (1.0)	0	3 (0.6)
Lung disorder	1.000	1 (0.3)	0	1 (0.2)
Lung infiltration NOS	1.000	1 (0.3)	0	1 (0.2)
Pneumonitis	1.000	1 (0.3)	0	1 (0.2)
Skin and appendages	0.039*	0	3 (1.9)	3 (0.6)
Hirsutism	0.039*	0	3 (1.9)	3 (0.6)

Table 26. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Study: Discontinued Study Treatment Permanently (AE, Inf, Mal)

Body System[a] Adverse Event	Overall p-Value	Treatment		
		SRL n=310	CSA n=161	Total N=471
Urogenital system	0.006**	13 (4.2)	0	13 (2.8)
Albuminuria	1.000	1 (0.3)	0	1 (0.2)
Kidney failure	0.549	2 (0.6)	0	2 (0.4)
Kidney function abnormal	1.000	1 (0.3)	0	1 (0.2)
Kidney tubular disorder	1.000	1 (0.3)	0	1 (0.2)
Kidney tubular necrosis	0.554	3 (1.0)	0	3 (0.6)
Sexual function abnormal	1.000	1 (0.3)	0	1 (0.2)
Urinary incontinence	0.549	2 (0.6)	0	2 (0.4)
Urinary tract disorder	0.554	3 (1.0)	0	3 (0.6)

Overall p-value: Fisher's Exact Test p-value (2-Tail).
Statistical significance at the 0.05, 0.01, 0.001 levels is denoted by *, **, *** respectively.
AEs = adverse events; CsA = cyclosporine; Inf. = infection; Mal = malignancy; N = total number of subjects; n = number of subjects in each treatment group; NOS = not otherwise specified; SRL = sirolimus.
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.

Deaths: Table 27 presents those deaths that occurred during the study by treatment group, subject number, days on study therapy, study day of death, and cause of death. In the ITT population, 10 (2.1%) subjects died during the study, 9 from Group A and 1 from Group B. The majority of deaths were attributed to infection. The length of time these subjects received therapy ranged from 5 to 190 days.

Death as a reason for discontinuation was reported in more subjects in Group A (3 subjects; 0.97%) compared with Group B (1 subject; 0.62%), although this difference was not statistically significant.

Table 27. Summary of Subjects Who Died and Cause of Death, by Treatment Group: ITT Population

Treatment Group Subject Serial No.	Days on Study Therapy	Study Day of Death	Cause of Death
Group A: (n=9)			
1.	190	211	Pulseless electrical activity
2.	58	79	Unknown
3.	41	43	Cardiac arrest
4.	62	80	Sepsis
5.	21	31	Cardiovascular insufficiency
6.	88	106	Cerebral abscess
7.	40	140	Multiorgan failure due to hemophagocytic syndrome and cytomegalovirus infection
8.	25	32	Organ failure/sepsis
9.	67	67	Feculent peritonitis; perforated sigmoid diverticulum; acute diverticulitis
Group B: (n=1)			
1.	5	5	Thrombotic thrombocytopenic purpura

ITT = intent-to-treat; n = number of subjects in each treatment group; No. = number.

CONCLUSIONS: This study was prematurely terminated because rates of BCAR were significantly greater in subjects treated with sirolimus compared with those receiving CsA, despite the additive effects of basiliximab, MMF, and corticosteroids. This imbalance persisted despite an amendment to the study to increase exposure to sirolimus so subjects met the protocol-mandated trough levels more quickly. The lower-than-expected rates of rejection seen in subjects receiving CsA could be secondary to the population, which was low to moderate risk, or to the monitoring of CsA concentration collected approximately 2 hours after dose administration (C_2), which was permitted in the study but not measured. Although most of these rejections were mild, the severity was significantly greater in subjects receiving sirolimus. Rates of graft loss were similar between groups but deaths were numerically greater in subjects receiving sirolimus. The incidence and duration of DGF were similar between treatment groups, but the incidence of delayed wound healing necessitating surgery was significantly greater in subjects receiving sirolimus. Sirolimus was associated with significantly more transplant rejection, diarrhea, thrombocytopenia, hyperlipemia, hypocalcemia, hypokalemia, pneumonia, aspartate aminotransferase/serum glutamic oxaloacetic increased, and albuminuria. Some of these events, such as anemia, diarrhea, and thrombocytopenia, may have been exacerbated by the concomitant use of MMF. Use of CsA was associated with significantly more infection, hyperuricemia, hypomagnesemia, osteoporosis, tremor, and hirsutism. Subjects receiving sirolimus had laboratory evidence of hyperlipidemia, hyperlipemia, and anemia and required more treatment with lipid-lowering and erythropoietic medications.

Monitoring concentrations of sirolimus, CsA, mycophenolic acid (MPA), and mycophenolic acid glucuronide failed to demonstrate differences in time-normalized trough concentration ($C_{min, TN}$) between those who experienced rejection, graft loss, or death and those who did not. MPA concentrations were variable but higher on average in subjects treated with sirolimus compared with those treated with CsA, despite direction to decrease doses.

In conclusion, when used from the time of transplantation in association with basiliximab, MMF, and corticosteroids, a sirolimus-based, CNI-free immunosuppressive regimen was associated with an unacceptably high rate of BCAR, and one that was significantly higher when compared with CsA-based immunosuppression, despite the addition of antibody induction.