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

PROTOCOL NO.: 0468H1-313 (B1741184)

PROTOCOL TITLE: A Randomized, Open-Label, Comparative Evaluation of Conversion From Calcineurin Inhibitor Treatment to Sirolimus Treatment Versus Continued Calcineurin Inhibitor Treatment in Liver Allograft Recipients Undergoing Maintenance Therapy

Study Centers: A total of 82 centers took part in study and enrolled subjects; 5 in Argentina, 4 in Australia, 1 in Austria, 2 in Brazil, 4 in Canada, 1 in Chile, 6 in France, 3 in Germany, 1 in Hong Kong, 4 in Italy, 2 in the Republic of Korea, 1 in Mexico, 1 in the Netherlands, 1 in New Zealand, 2 in Portugal, 7 in Spain, 2 in Switzerland, 1 in Taiwan, 3 in the United Kingdom, and 31 in the United States.

Study Initiation Date and Final Completion Dates: October 2002 to July 2008.
In November 2006 enrollment was complete; however, this 6-year study was terminated early in July 2008, because the co-primary endpoints for efficacy and safety were not met (based on interim analysis with the data cutoff date of December 2007).

Phase of Development: Phase 3

Study Objective:

Primary Objective: To demonstrate the following, in stable liver transplant recipients:

- Superiority of the Sirolimus (SRL) conversion regimen over the calcineurin inhibitor (CNI) continuation regimen with regard to the change from Baseline in glomerular filtration rate (GFR) (Cockcroft-Gault method) at 12 months. The comparison was to be performed on an intent-to-treat (ITT) basis (incorporating calculated GFRs for all subjects for whom a 12-month creatinine value was available)

- Non-inferiority of the SRL conversion regimen with regard to the rate of the first occurrence of graft loss or death at 12 months in the ITT population

Secondary Objectives: To compare the following between the 2 treatment groups (SRL conversion versus (vs) CNI continuation):

- Incidence of biopsy-confirmed acute rejection

- Subject survival and graft survival

- Change in creatinine values in the ITT and On-Therapy populations
- GFR values calculated by the methods of Cockcroft-Gault and Levey, and measured GFR values for the ITT and On-Therapy populations
- Slope of the regression line for a plot of 1/creatinine and GFR values versus time
- Incidence of treatment failure (defined as the first occurrence of acute rejection or premature discontinuation for any reason)
- Mean systolic and diastolic blood pressures and mean arterial pressure
- Percentage of subjects requiring treatment for hypertension and number of antihypertensive agents used
- Quality of life outcomes
- Changes in hepatic fibrosis score over time
- Incidence of malignancy and clinically important infection; and
- Long-term safety for up to 6 years.

METHODS

Study Design: This was an open-label, stratified (hepatitis C virus [HCV] status, antimetabolite therapy), randomized, parallel-group, comparative, outpatient study in stable liver transplant recipients, to evaluate the impact of immunosuppressive maintenance therapy on renal function after conversion from CNI- to SRL-based therapy (ie, SRL conversion), compared with continued CNI therapy (ie, CNI continuation).

Within 30 days before the randomization, eligible subjects were stratified by HCV status (ie, HCV positive/negative, as determined by polymerase chain reaction [PCR]) and by antimetabolite therapy (ie, with/without therapy with azathioprine [AZA] or mycophenolate mofetil [MMF]), followed by randomized (2:1 ratio [SRL:CNI]) to receive either CNI continuation therapy (Group A) or SRL conversion (Group B) as immunosuppressive maintenance therapy.

The total study duration was planned to be approximately 10 years: with an approximate 4-year enrollment period. Each subject was to have been followed for a 72-month treatment phase, with a 1-month safety follow-up after last study treatment (Month 73).

A flow chart of study procedures is provided in Table 1 and Table 2, for discontinued subjects in Table 3, and the flow diagram for stratification by pre-transplantation HCV status is summarized in Figure 1.

Table 1. Study Flow Chart 1: The First 24-Month Treatment (to be continued in Study Flow Chart 2, Table 2)

Procedure/Assessment	Screening Baseline[a]	Day 1[b]	Day 7	Day 14	Day 28	Day 42	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24
Visit ID	**1**	**2**	**3**	**4**	**5**	**5.5**	**6**	**7**	**8**	**10**	**11**	**13**	**14**
Study Visit Window (days)			**±2**	**±2**	**±7**	**±6**	**±7**	**±7**	**±14**	**±14**	**±21**	**±21**	**±21**
Test article administration[c]		To be administered from Day 1 through Month 24											
Medical history	X												
Complete physical examination[d]	X								X		X	X	X
Limited physical examination				X	X		X	X					
Adverse event monitoring[e]	Ongoing collection of adverse events												
Chest radiograph[f]	X	As clinically indicated							X	As clinically indicated			X
Pregnancy test[g]	X	As clinically indicated											
Hematology and chemistry values[h]	X		X	X	X		X	X	X	X	X	X	X
LDL- and HDL-cholesterol values[h]	X				X			X	X		X	X	X
Coagulation profile[h]	X				X			X	X		X	X	X
Urine for protein/creatinine[i]	X							X	X		X	X	X
Measured GFR[j]	X								X		X	X	X
CMV antibody[k]	X	As clinically indicated											
Hepatitis C genotype and RNA concentration[l]	X	X						X	X		X	X	X
Doppler liver ultrasound[m]	X	As clinically indicated											
Liver biopsy (all centers)[n]	X	As clinically indicated											
Liver biopsy (centers performing periodic biopsies)[o]	Per the subject's predetermined schedule												
Pharmacokinetic analysis (participating centers only)[p]					X			X					
SRL whole-blood trough levels[q]		X	X	X	X	X	X	X	X	X	X	X	X
CNI whole-blood trough levels[r]		X	X	X	X		X	X	X	X	X	X	X
Acute rejection							X		X		X	X	X
Subject and graft survival									X		X	X	X
Quality of life questionnaire[s]		X							X		X		X

AE = adverse event; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor, CORE = Computerized Randomization / Enrollment; CRF = case report form; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LFT = liver function test; LFR = liver function reserve; PCR = polymerase chain reaction; PE = physical examination; PK = pharmacokinetics; RNA = ribonucleic acid; SAE = serious adverse event; SRL = sirolimus.

a. Screening / Baseline: To be performed within 14 days before randomization. Reminder: The last 5 values for serum creatinine that were obtained before screening (at ≥monthly intervals) must be recorded on the CRFs along with the date obtained (excluding values obtained during an acute event that may

Table 1. Study Flow Chart 1: The First 24-Month Treatment (to be continued in Study Flow Chart 2, Table 2)

affect serum creatinine).

b. Day 1: Day when first dose of test article is administered (≤24 h after CORE randomization).
c. Test article administration: Per randomization. SRL dosage adjustment.
d. PE: Complete PE, include weight, sitting blood pressure (twice), heart rate, temperature and complete body system assessment. Height was measured at Screening/Baseline. A limited PE was including cardiovascular, abdominal and neurological exams, and weight, sitting blood pressure (twice), temperature, and heart rate.
e. Adverse event monitoring: All adverse events and serious adverse events were collected continuously from the time informed consent is signed through Month 73. Adverse events was recorded on the CRFs at each study visit except study Day 7 and study Day 42.
f. Chest Radiograph: Screening posteroanterior and lateral view chest radiograph may be obtained within 3 months before randomization.
g. Pregnancy test: Serum pregnancy test is for women of childbearing potential only.
h. Hematology, chemistry, LDL and HDL-cholesterol, and coagulation profile values
i. Urine for protein/creatinine: Random morning urine void preferred for protein and creatinine concentrations. First morning urine void may not be used for this laboratory determination. A 24-hour urine collection may also be used.
j. Measured GFR: Performed only at centers that elect to measure GFR. Screening measured GFR may be obtained within 4 weeks before randomization
k. CMV antibody: Does not need to be repeated if previously documented as positive.
l. Hepatitis C: Antibody testing must be performed locally at Screening. If not performed within 30 days of random purpose of randomization stratification. Hepatitis C genotype and RNA concentration to be measured at a Sponsor-designated central laboratory for PCR positive subjects only.
m. Doppler liver ultrasound: Screening Doppler ultrasound must be obtained within 4 weeks before randomization.
n. Liver biopsy: Subjects were required to have a liver biopsy at any time to rule out rejection if their LFRs increase >2 x their baseline value and persist on a repeat determination made within 48 hours unless a clear alternative etiology is apparent for elevated LFTs.
o. Liver biopsy (at centers performing periodic biopsies only): In addition to the Screening biopsy, biopsy evaluations were collected from subjects at centers who perform them periodically as part of their routine follow-up.
p. PK analysis (participating centers): All subjects randomized to Group B were invited to participate in the PK analysis and were asked to sign a separate PK analysis informed consent form, prior to Day 28 and Month 3 blood sample collection for PK analysis.
q. SRL whole-blood trough levels: Subjects in Group B only. To be collected before the daily administration of SRL and 24±2 hours after the last dose of SRL. Sample collection on Day 42 is at the discretion of the Investigator to ensure the target range is achieved and is strongly recommended for subjects clinically indicated. Samples were also being collected after all SRL dose adjustments, whenever possible at the time of any drug-related AE or suspected acute rejection. Additional samples may be collected at the discretion of the Investigator. Subjects who cannot be maintained in the target range (8 to 16 ng/mL) should have SRL discontinued.
r. CI whole-blood trough levels: Subjects in Group A only. CI whole-blood trough levels will be obtained 12±2 hours after the previous evening dose and before the morning dose. Sample will be collected after all CI dose adjustment and whenever possible at the time of any drug-related AE or suspected acute rejection. Additional sample may be collected at the discretion of the Investigator. Subjects who cannot be maintained in the target range should discontinue from the study.
s. Quality of life questionnaire: Day 1 assessment must be performed within 24 hours after random assignment and should be performed before administration of first dose of test article.

Table 2. Study Flow Chart 2: Subjects Continuing Study Medication After Month 24 and up to Month 72

Procedure/Assessment	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	Month 66	Month 72	Month 73 Follow-Up[a]
Visit ID	**17**	**19**	**21**	**22**	**24**	**25**	**27**	**28**	**30**
Study Visit Windows (days)	**+21**	**+21**	**+21**	**+21**	**+21**	**+21**	**+21**	**+21**	**+7**
Test article administration[b]	To be continued through Month 72								
Complete physical examination[c]	X		X		X		X		
Limited physical examination[c]		X		X		X		X	
Adverse event monitoring[d]	Ongoing collection of adverse events								
Chest radiograph[e]	As clinically indicated								
Pregnancy test[f]	As clinically indicated								
CBC, haematology and chemistry values	X	X	X	X	X	X	X	X	X
LDL and HDL cholesterol values	X	X	X	X	X	X	X	X	X
Coagulation profile[g]	As clinically indicated								
Urine for protein/creatinine[h]	X	X	X	X	X	X	X	X	
CMV antibody	As clinically indicated								
Doppler ultrasound of liver	As clinically indicated								
Liver biopsy (all centres)	As clinically indicated								
Liver biopsy (periodic biopsies)[i]	Per the subject's predetermined schedule								
SRL whole-blood trough levels[j]	X	X	X	X	X	X	X	X	
CNI whole-blood trough levels[k]	X	X	X	X	X	X	X	X	
Acute rejection	X	X	X	X	X	X	X	X	X
Subject and graft survival	X	X	X	X	X	X	X	X	X

CBC = complete blood count; CMV = cytomegalovirus; CNI = calcineurin inhibitor, CRF = case report form; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PE = physical examination; SRL = sirolimus.

a. Month 73 Follow-up Visit: was performed 4 weeks (±7 days) following the Month 72 visit.
b. Test article Administration: Subjects to continue on the same test article regimen as randomized.
c. PE: Complete PE included weight, sitting blood pressure (twice), heart rate, temperature and complete body system assessment. A limited PE included cardiovascular, abdominal and neurological exams and weight, sitting blood pressure (twice), temperature and heart rate.
d. Adverse event monitoring: All adverse events and serious adverse events were collected continuously from the inform consent is signature- through Month 73. Adverse events were recorded on the CRFs at each study visit.
e. Chest radiograph: Posteroanterior and lateral view chest radiograph may be obtained whenever clinically indicated.
f. Pregnancy test: Serum pregnancy test is for women of childbearing potential only.
g. CBC, haematology, lipid and coagulation profile values.
h. Urine for protein/creatinine: Random morning urine void is preferred for protein and creatinine concentrations. First morning urine void may not be used for

Table 2. Study Flow Chart 2: Subjects Continuing Study Medication After Month 24 and up to Month 72

this laboratory determination. A 24-hour urine collection method may also be used.

i. Liver biopsy (centres performing periodic biopsies): Routine biopsies were performed as per subject's predetermined schedule.

j. SRL whole-blood trough levels: Subjects in Group B only. To be collected before the daily administration of SRL and 24±2 hours after the last dose of SRL. Samples were also to be collected after all SRL dose adjustments, whenever possible at the time of any drug-related AE or suspected acute rejection. Additional samples may be collected at the discretion of the Investigator. Subjects who cannot be maintained in the target range (8 to 16 ng/mL) by chromatographic method or 10-20 ng/mL by immunoassay should have SRL discontinued.

k. CNI whole-blood trough levels: Subjects in Group A only. CNI whole-blood trough levels were obtained 12±2 hours after the previous evening dose and before the morning dose. Samples were collected after all CNI dose adjustments, and whenever possible at the time of any drug-related AE or suspected acute rejection. Additional samples may be collected at the discretion of the Investigator. Subjects who cannot be maintained in the target range should discontinue from the study.

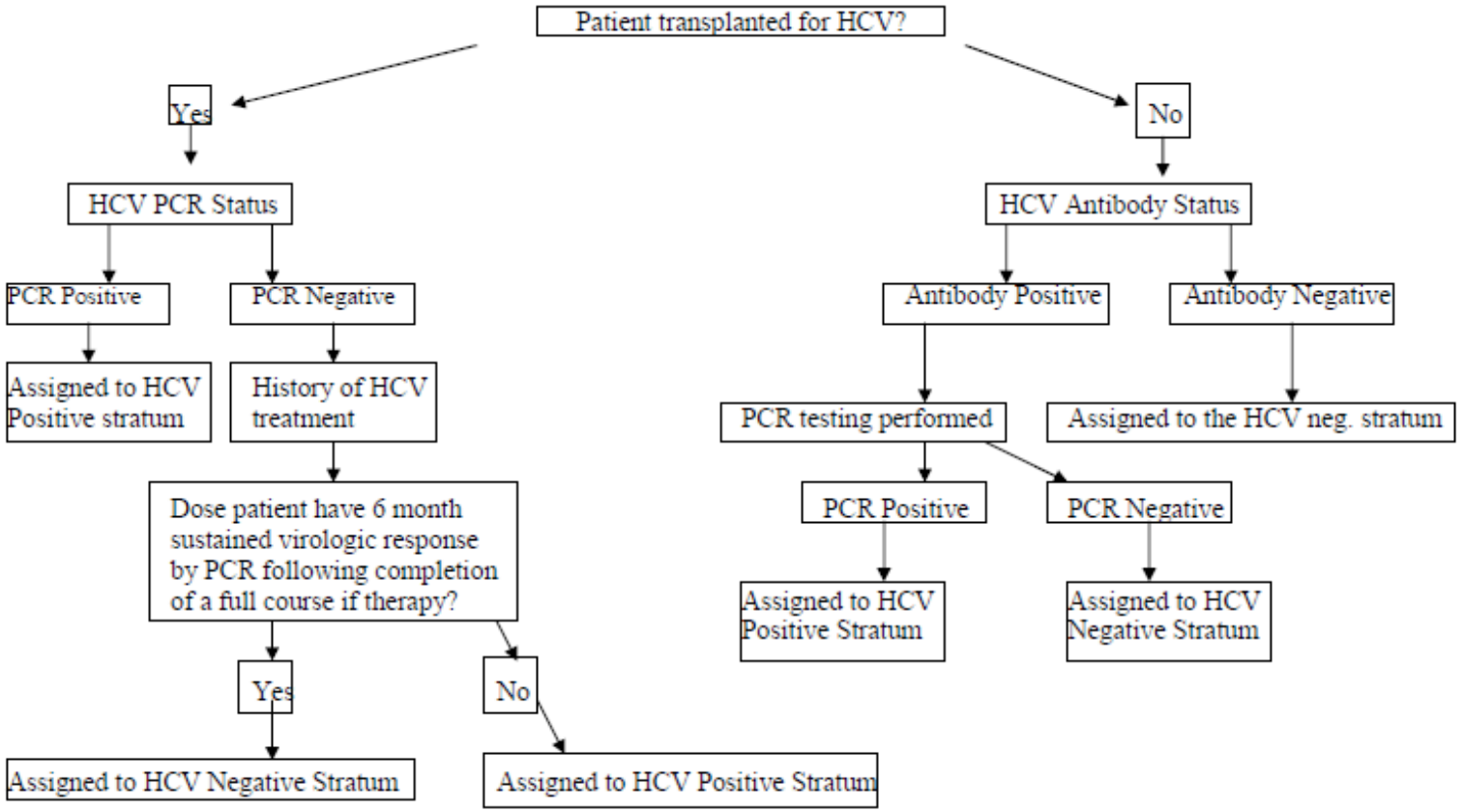
Table 3. Study Flow Chart 3: Discontinued Subject Visits[a]

	Time of Discontinuation (Within 1 Week of Discontinuation)	1 Month After Discontinuation	6	12	24	30	36	48	60
			Months After Randomization						
Visit ID	**98**	**99**				**18**	**20**	**23**	**26**
Study Visit Window (Days)	**+7**	**+7**	**±14**	**±21**	**±21**	**+21**	**+21**	**+21**	**+21**
Complete physical examination[b]	X								
Adverse Event Monitoring[c]	All events		Limited events						
Chest radiograph	To be obtained whenever clinically indicated								
Pregnancy test	To be obtained whenever clinically indicated								
Hematology and chemistry values[d]	X	X	X	X	X				
Limited chemistry values and weight[d]						X	X	X	X
LDL- and HDL-cholesterol values[d]	X	X	X	X	X				
Coagulation profile[d]	X	X							
Urine for protein/creatinine[e]	X		X	X	X	X	X	X	X
Acute rejection	X	X	X	X	X	X	X	X	X
Subject and graft survival	X	X	X	X	X	X	X	X	X
SRL whole-blood trough levels[f]	X								
CNI whole-blood trough levels[g]	X								
Quality of Life questionnaire	X								

AE = adverse event; BUN = blood urea nitrogen; CNI = calcineurin inhibitor; DC = discontinuation; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SAE = serious adverse event; SRL = sirolimus.

a. When a subject discontinues test article, a DC study visit were completed within 1 week. A second DC visit should be completed at 1 month following the discontinuation. The subsequent study visits were determined by using the next closest timepoint from the date of random assignment, ie, 6, 12, 24 months etc. following random assignment.
b. To include weight, sitting blood pressure (twice), temperature and complete body system assessment.
c. All AEs and SAEs were collected continuously from the time of discontinuation of assigned treatment and through 1 month after discontinuation. Limited AE and SAE monitoring was performed from 1 month after discontinuation through month 72 after random assignment. Limited AEs were include acute rejections, graft loss, death, malignancy and those infections that meet the criteria for a serious adverse event. All female subjects were followed up for pregnancy for 3 months after the discontinuation of test articles.
d. Hematology, chemistry, cholesterols and coagulation profile evaluations. Limited chemistry evaluations included serum creatinine, BUN, Albumin and weight (for calculated GFR only).
e. Random morning urine void preferred for protein and creatinine concentrations. First morning urine void may not be used for this laboratory determination. A 24-hour urine collection method may also be used.
f. Subjects in Group B only. To be collected within 1 week after the last dose of SRL.
g. Subjects in Goup A only. To be collected within 1 week after the last dose of CNI.

Figure 1. Flow Diagram for Stratification by Hepatitis C Status



HCV = hepatitis C virus; PCR = polymerase chain reaction.

Number of Subjects (Planned and Analyzed): Approximately 600 subjects were planned to be enrolled (approximately 200 subjects in the CNI group and 400 subjects in the SRL group). A total of 607 subjects were enrolled, stratified to the following strata: receiving antimetabolite therapy + hepatitis C negative (215 subjects), receiving antimetabolite therapy + hepatitis C positive (20 subjects), not receiving antimetabolite therapy + hepatitis C negative (318 subjects), and not receiving antimetabolite therapy + hepatitis C positive (54 subjects), and were randomized to study drug (393 subjects to SRL conversion and 214 subjects to CNI continuation). The subjects were stratified. All 607 subjects were included in the ITT analyses; the safety population (subjects who received at least 1 dose of study medication at a pre-defined time point) included 599 subjects, 389 in the SRL conversion cohort and 210 in the CNI continuation cohort.

Diagnosis and Main Criteria for Inclusion: Male and female subjects, age ≥13 years (age >18 years as required by some local regulations) and weight ≥40 kg, within 6 to 144 months after their orthotropic liver transplantation, receiving immunosuppressive therapy with stable CNI doses, or with a combination of CNI with corticosteroids and/or antimetabolite for ≥4 weeks prior to randomization, having Cockcroft-Gault GFR values ≥40 mL/min and ≤90 mL/min at Screening and the subject's Doppler ultrasonography (performed within 4 weeks before randomization) showed no evidence of thrombosis or of clinically significant stenosis of the hepatic artery, hepatic vein, or portal vein.

Excluded were subjects who had history of nonhepatic transplantation, subjects with any evidence of rejection or treatment for suspected rejection within 3 months prior to randomization, subjects with prior or current use of SRL, subjects with a known or suspected malignancy (other than skin malignancy) <5 years before randomization, subjects with evidence of systemic infection (eg, sepsis, bacteremia, pneumonia) and subjects with stage 4, 5, or 6 liver fibrosis, or signs of decompensation of the current liver allograft.

Study Treatment: After stratification, subjects in each of the 4 strata were randomized (1:2 ratio) to Group A (CNI continuation) or Group B (SRL conversion), to receive study drug as outlined below. Study drug administration started on Day 1 and could be continued through Month 72 (24 months in the initial phase and a further 48 months in the safety extension).

Group A (Calcineurin Inhibitor Continuation)

Tacrolimus (TAC) or cyclosporine (CsA) was administered per local practice to attain target trough levels of 3 to 10 ng/mL or 50 to 250 ng/mL, respectively. Subjects were permitted to convert from TAC to CsA, or vice versa, at any point during the study, at the discretion of the Investigator. The date of any such conversion was recorded as well as the reason for the conversion.

Group B (Sirolimus Conversion)

SRL was administered once daily as tablets of 1, 2, or 5 mg, as prescribed by the Investigator. SRL oral solution at 1 mg/mL could be provided only to subjects who were

unable to tolerate the tablet formulation, as prescribed by the Investigator, following approval by the Medical Monitor.

A loading dose of SRL, 10 to 15 mg, was administered in divided doses on Day 1: the first dose was given after collection of the SRL trough level and a minimum of 4 hours following the last dose of CNI, and the second dose approximately 12 hours after the first dose. On Days 2 through 6, SRL was administered in a dose of 3 to 5 mg/day. For the remaining study period, Day 7 through Month 72, appropriate daily doses of SRL were administered to attain the recommended trough concentrations of 8 to 16 ng/mL (using a chromatographic method) or 10 to 20 ng/mL (using an immunoassay).

Concomitant Corticosteroids Treatment: Subjects in either group who had been receiving CS during the 4 weeks before randomization were required to continue receiving CS for the first 90 days on study medication. After 90 days, CS could be eliminated, restarted, or discontinued at the discretion of the Investigator. Subjects not receiving CS at the time of randomization could start CS as treatment for an acute rejection episode, which could then be continued or discontinued at the discretion of the Investigator.

Concomitant Antimetabolite Therapy: MMF or AZA could be administered to subjects in either treatment group. Subjects could continue to receive MMF or AZA only if they had been receiving this therapy daily for ≥4 weeks before randomization. MMF or AZA could be initiated in either group, even if the subject had not been receiving antimetabolite therapy at the time of randomization in the following cases: 1) at the time of acute rejection or 2) for toxicity necessitating the reduction of the CNI (Group A) or SRL (Group B). Antimetabolite therapy could be stopped and restarted and subjects could convert from MMF to AZA, or vice versa, at the discretion of the Investigator.

Efficacy and Safety Endpoints:

Primary Endpoints:

1. The change from Baseline in calculated GFR (Cockcroft-Gault method) at 12 months in the ITT population (incorporating calculated GFRs for all subjects for whom a Month 12 creatinine value is available)

2. The rate of the first occurrence of graft loss or death at 12 months in the ITT population

Secondary Endpoints:

1. Incidence of biopsy-confirmed acute rejection at 2, 6, 12, 24, 36, 48, 60, and 72 months

2. Subject survival at 12, 24, 36, 48, 60, and 72 months

3. Graft survival at 12, 24, 36, 48, 60, and 72 months

4. Change from Baseline in creatinine at 6, 12, 24, 36, 48, 60, and 72 months and Cockcroft-Gault GFR at 6, 24, 36, 48, 60, and 72 months (ITT population)

5. Change from Baseline in creatinine and Cockcroft-Gault GFR at Months 12 and 24-modified ITT analysis. Subjects with missing creatinine and Cockcroft-Gault GFR values at Months 12 and 24 was their last available values carried forward

6. Change from Baseline in serum creatinine and Cockcroft-Gault GFR. For all subjects continuing with therapy at 6, 12, 24, 36, 48, 60, and 72 months

7. Change from Baseline in serum creatinine and Cockcroft-Gault GFR (modified on therapy). All subjects randomly assignment to treatment where, if an on therapy Month 12 and/or 24 creatinine value is missing, the last On-therapy observation recorded was carried forward (LOCF analysis 2)

8. Change from Baseline in measured GFR at 6, 12, 18, and 24 months for all subjects randomized to treatment at those centers which elected to perform measured GFR, and all subjects at these centers remaining on therapy at the specified time points

9. Change from Baseline in GFR values calculated by the method of Levey at Months 6, 12, 24, 36, 48, 60, and 72 (ITT and On-therapy populations)

10. Slope of the regression line for a plot of 1/creatinine and GFR values versus time at Months 6, 12, and 24. (ITT and On-therapy)

11. Incidence of treatment failure (defined as the first occurrence of acute rejection or premature discontinuation for any reason) at Months 6, 12, and 24

12. Change from Baseline in mean systolic and diastolic blood pressure and mean arterial pressure for all subjects continuing with therapy at 12, 24, 36, 48, 60 and 72 months

13. Change from Baseline in the percentage of subjects requiring treatment for hypertension and in the number of antihypertensive agents administered at 12 and 24 months (ITT and On-therapy populations)

14. Incidence of Malignancy and clinically important infection at 12 and 24 months and yearly are to be examined in a subset of subjects

15. Changes in Hepatic Fibrosis Score (Banff 1997) for hepatitis C positive subjects at selected centers at Months 12 and / or 24 at time of biopsy

16. Quality of life outcomes at 6, 12, and 24 months.

Safety Evaluations: Subjects were monitored throughout the study for the occurrence of infections, lymphoproliferative disease, other malignancies, stomatitis, and other AEs and SAEs. Physical examination, weight, vital signs, safety laboratory values (including HCV analyses) as summarized in Table 1. Subjects who developed oral lesions after randomization were appropriately diagnosed and followed-up to clarify etiology.

Statistical Methods: The following populations of enrolled subjects were defined and used in the statistical analysis of the study data.

Intent-To-Treat Population (ITT): For the renal function part of the primary endpoint, the ITT population consists of all subjects randomized to treatment. For the subject and graft survival part of the primary endpoint, any subject lost to follow-up (missing) at 12 months is counted in the analysis of subject survival or graft survival as an event (ie death or graft loss) and classified as "missing".

Modified Intent-To-Treat Population (mITT): The modified intent-to-treat population (mITT) or "safety" population consists of all subjects who had received at least 1 dose of study medication.

On-Therapy Population: The On-Therapy population consists of subjects who were still receiving study medication at a pre-defined time point.

All-Visits analyses: The All-Visits analyses include On-Therapy data and follow-up data collected after the termination of study medication. Data from subjects who discontinued treatment with study medication but remained in the study and were followed according to a modified follow-up schedule are included in this group.

Statistical analyses were based on the data from all clinical study sites. Unless otherwise stated, the use of the word "significant" in conjunction with the results refers to p-value <0.05, and all tests were 2-tailed.

The primary efficacy analysis was an analysis of covariance (ANCOVA) fitting treatment, antimetabolite therapy status, and hepatitis C status (by PCR) as fixed effects and fitting baseline Cockcroft-Gault GFR value as covariate in the ITT population. Summary statistics included adjusted least squares means of the Month 12 GFR by antimetabolite therapy and hepatitis C status, and by treatment. The estimated differences in the Month 12 baseline-adjusted mean GFR between treatments and the corresponding 2-sided 95% confidence intervals (CIs) were computed. The superiority of SRL therapy compared with standard CNI therapy was to be declared if the lower confidence limit of the 95% CI for the difference in adjusted mean GFR was >0. A second model with treatment as a fixed factor and center as a random factor, and including treatment by center interaction, was to be investigated to explore the possibility of qualitative or quantitative treatment by center interaction if there was a significant treatment effect. Uniformity of efficacy across randomization strata was assessed by investigating the effect of the treatment-by-antimetabolite therapy, and treatment-by-antimetabolite therapy-by-hepatitis C interactions in separate models. If any clinically and statistically significant treatment by strata interaction were found, the efficacy results were analyzed and interpreted separately by each stratum. Sensitivity analyses were performed by omitting subjects with "problematic" data. Problematic data included subjects who died or had graft loss before 12 months or who were missing their Month 12 visit data.

The primary analysis for the subject/graft survival (safety) was performed using the Cochran-Mantel-Haenszel (CMH) procedure with stratification by antimetabolite therapy

status and hepatitis C status (positive or negative, as determined by PCR) in the ITT population. Summary statistics (frequency and crude incidence rate) were reported by treatment. The adjusted difference in the rates of the primary safety endpoint between treatments (rate of Group B minus Group A), with the corresponding 2-sided stratified 95% CI, was provided. The Breslow-Day statistics were used to test homogeneity of association for the strata employed in the CMH analysis. The objective of the analysis was to demonstrate non-inferiority of the SRL conversion regimen over the CNI continuation regimen with respect to the primary safety endpoint. A positive difference in the rates of graft survival (rate of Group B minus Group A) favors Group B. If the lower confidence limit of the 95% CI for the difference in rates of subject and graft survival, rate in Group B (SRL therapy) minus rate in Group A (standard therapy), was no less than -0.05, then non-inferiority of SRL therapy to best local therapy was declared. The delta was selected to reflect the importance of the graft survival endpoint.

The focus of analyses of secondary endpoints was on 2 and 6 months and 1 and 2 years. For binary endpoints (rejection, graft survival, and subject survival) that were determined after 2 years during the extended treatment phase of the study, only the Fisher exact test and simple CIs of the difference in rates were to be calculated. For continuous endpoints that occur after 2 years (eg, creatinine and Cockcroft-Gault GFR), ANCOVA values for On-Therapy subjects with treatment as factor were to be calculated. For these analyses, the population of all subjects who elected to continue after the initial 2 years formed the basis of these analyses in a subsequent report of data beyond Month 12.

Analysis of variance (ANOVA) methods were to be used to test whether subjects experiencing adverse reactions had different SRL, CsA, or TAC concentrations, calculated above, than subjects who did not experience the adverse reaction in question. Logistic regression analysis was to be used to test whether SRL, CsA, or TAC concentrations contributed to the risk of occurrence of the adverse reactions in question.

Because the study was terminated early, well before all subjects had the opportunity to complete the intended 72-month study duration, the following planned analyses were not performed: change from Baseline in measured GFR and Levey-calculated GFR, liver histopathology (hepatic fibrosis score), and quality of life assessment.

RESULTS

Subject Disposition and Demography: A total of 607 subjects were enrolled: 393 subjects were randomized to the SRL conversion Group B and 214 subjects to the CNI continuation Group A. Of these 607 subjects, 599 (389 in the SRL conversion cohort and 210 in the CNI continuation cohort) received at least 1 dose of study medication.

The distribution of ITT subjects across the 4 strata is provided in Table 4.

Table 4. Distribution Across the 4 Strata – ITT Population

Strata, n (%)	SRL Conversion (N=393)	CNI Continuation (N=214)	Total (N=607)
Receiving antimetabolite therapy	149 (37.91)	86 (40.19)	235 (38.71)
Hepatitis C positive	47 (11.96)	27 (12.62)	74 (12.19)
Receiving antimetabolite therapy + hepatitis C negative	139 (35.37)	76 (35.51)	215 (35.42)
Receiving antimetabolite therapy + hepatitis C positive	10 (2.54)	10 (4.67)	20 (3.29)
Not receiving antimetabolite therapy + hepatitis C negative	207 (52.67)	111 (51.87)	318 (52.39)
Not receiving antimetabolite therapy + hepatitis C positive	37 (9.41)	17 (7.94)	54 (8.90)

CNI = calcineurin inhibitor; ITT = intent-to-treat; SRL = sirolimus.

The primary reasons for discontinuation of dose administration are shown in Table 5.

Table 5. Number (%) of Subjects Who Discontinued Dose Administration by Primary Reason

Conclusion Status Reason[a]	Overall p-Value[b,c]	Treatment		
		SRL (CONC CTRL) n=389	CNI Continuation n=210	Total n=599
Discontinued[c]		380 (97.69)	196 (93.33)	576 (96.16)
Adverse event	<0.001***	128 (32.90)	25 (11.90)	153 (25.54)
Failed to return	0.001**	1 (0.26)	8 (3.81)	9 (1.50)
Other non-medical event[c]		198 (50.90)	144 (68.57)	342 (57.10)
Subject request unrelated to study	1.000	22 (5.66)	12 (5.71)	34 (5.68)
Protocol violation	0.410	19 (4.88)	7 (3.33)	26 (4.34)
Unsatisfactory response - efficacy	0.011*	12 (3.08)	0	12 (2.00)

CNI = calcineurin inhibitor; CONC = concentration; CTRL = control; SRL = sirolimus.

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

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

c. The category of "Other Non-medical Event" also includes subjects whose dose administration was discontinued because of closure of the study site at which they were enrolled, as well as subjects whose dose administration was discontinued for reasons not fitting one of the other categories. In light of this, p-values are not presented for the overall number of subjects who discontinued, or for subjects who discontinued due an "Other Non-medical Event."

A summary of the subject demography of the ITT population is presented in Table 6.

Table 6. Demographic and Baseline Characteristics of the ITT Population

Characteristic	p-Value	Treatment		
		SRL Conversion (n=393)	CNI Continuation (n=214)	Total (n=607)
Age				
N		393	214	607
Mean	0.405[a]	55.37	54.69	55.13
Standard Error		0.48	0.66	0.39
Minimum		23.00	21.00	21.00
Maximum		76.00	73.00	76.00
Median		57.00	56.50	57.00
Sex	0.783[b]			
Female		122 (31.04)	64 (29.91)	186 (30.64)
Male		271 (68.96)	150 (70.09)	421 (69.36)
Ethnic origin	0.323[b]			
Other: NZ Maori			1 (0.47)	1 (0.16)
Black		20 (5.09)	6 (2.80)	26 (4.28)
Hispanic		8 (2.04)	9 (4.21)	17 (2.80)
Oriental(Asian)		43 (10.94)	20 (9.35)	63 (10.38)
Other		8 (2.04)	5 (2.34)	13 (2.14)
Other: NZ European		1 (0.25)	0	1 (0.16)
White		313 (79.64)	173 (80.84)	486 (80.07)
Baseline height				
N		360	197	557
Mean	0.344[a]	169.19	170.02	169.48
Standard error		0.51	0.73	0.42
Minimum		144.00	146.00	144.00
Maximum		196.50	194.31	196.50
Median		170.00	171.50	170.00
Missing		33	17	50
Baseline weight				
N		360	197	557
Mean	0.278[a]	78.53	80.17	79.11
Standard Error		0.90	1.21	0.72
Minimum		40.00	47.00	40.00
Maximum		143.79	125.70	143.79
Median		76.11	80.00	78.06
Missing		33	17	50

ANOVA = analysis of variance; CNI = calcineurin inhibitor; ITT = intent-to-treat; N = total number of subjects in each treatment group; n = number of subjects in specified category; NZ = New Zealand; SRL = sirolimus.
a. One-way ANOVA with treatment as factor.
b. Fisher exact test p-value (2-tail).

Efficacy Results:

Primary Efficacy Endpoint Results:

The primary efficacy endpoint was the change from Baseline in calculated GFR (Cockcroft-Gault method) at 12 months in the ITT population (incorporating calculated GFRs for all subjects for whom a Month 12 creatinine value was available). The main goal of the primary efficacy endpoint was to test for superiority of SRL therapy compared with the standard therapy.

Please note that the coprimary endpoint for safety is presented in the Safety Results section of this PDS.

The ITT analysis of the primary efficacy endpoint, the change in baseline-adjusted mean Cockcroft-Gault GFR at Month 12, is presented in Table 7.

Table 7. Change From Baseline in Cockcroft-Gault GFR at Month 12 (ITT Population)

Cockcroft-Gault GFR, mL/min	Treatment[a]	
	SRL Conversion (n=393)	CNI Continuation (n=214)
Change from Baseline of the adjusted mean ± SE	-4.45±1.12	-3.07±1.36[b]
Maximum	49.67	45.85
75th Percentile	6.75	6.00
50th Percentile	-0.92	0.24
25th Percentile	-9.98	-7.72

ANCOVA = analysis of covariance; CNI = calcineurin inhibitors; GFR = glomerular filtration rate; ITT = intent-to-treat; n = number of subjects; PCR = polymerase chain reaction; SE = standard error; SRL = sirolimus.

a. Mean value of calculated Cockcroft-Gault GFR for all values where there was a valid baseline. Adjusted for baseline value; antimetabolite therapy status and hepatitis C status (by PCR) entered as fixed effects.
b. Rank ANCOVA p-value=0.342.

The results of the rank ANCOVA confirmed the absence of a significant difference in adjusted Cockroft-Gault GFR between treatment groups (Table 8).

Table 8. Change From Baseline in Cockcroft-Gault GFR at Month 12 Rank Analysis (ITT Population)

	Treatment[a]	
	SRL Conversion (n=393)	CNI Continuation (n=214)
Adjusted rank, mean ± SE	299.69±12.25	313.72±14.51[a]
Difference in Month 12 renal function (95% CI)[b]	14.03 (-14.96, 43.01)	

ANCOVA = analysis of covariance; CI = confidence interval; CNI = calcineurin inhibitors; GFR = glomerular filtration rate; ITT = intent-to-treat; n = number of subjects; SE = standard error; SRL = sirolimus.

a. p-Value from ANCOVA analysis adjusting for treatment, study strata, and baseline GFR: 0.342.
b. CNI continuation – SRL conversion.

Secondary Efficacy Endpoints:

Cockcroft-Gault Glomerular Filtration Rate at Month 12 With Last Observation Carried Forward

At Month 12 (Table 9), the change from Baseline adjusted Cockcroft-Gault GFR with LOCF was -0.06 and -0.26 mL/min for the SRL conversion and CNI continuation cohorts, respectively. The difference was not statistically significant (p=0.879).

Table 9. Change From Baseline in Cockcroft-Gault GFR at Month 12 (LOCF 1 Analysis)

Cockcroft-Gault GFR, mL/min	Treatment[a]	
	SRL Conversion (n=395)	CNI Continuation (n=214)
Change from baseline of the adjusted mean[a] ±SE	-0.06±1.10	-0.26±1.31[b]
Difference (95% confidence interval)	-0.2 (-2.82, 2.41)	

ANCOVA = analysis of covariance; CNI = calcineurin inhibitor; GFR = glomerular filtration rate; n = number of subjects; SE = standard error;

a. Mean value of calculated Cockcroft-Gault GFR for all values where there was a valid baseline. Adjusted for baseline value; antimetabolite therapy status, and hepatitis C status (by PCR) entered as fixed effects.
b. p-Value from ANCOVA analysis adjusting for treatment, study strata, and baseline GFR=0.879.

Observed Cockcroft-Gault Glomerular Filtration Rate – Subjects Remaining on Assigned Therapy

Mean values for observed Cockcroft-Gault GFR over time are presented in Table 10.

Table 10. Observed Mean (± Std) Cockcroft-Gault GFR (mL/min): On Therapy

Time (After Randomization)	--------SRL Conversion-------- N	Observed Mean	Std	------CNI Continuation----- N	Observed Mean	Std	Between-Group p-Value[a,b]
Baseline[c]	362	65.36	18.71	203	65.48	19.57	
Day 28	355	70.79	22.86	197	66.38	18.14	<0.001***
Study Month 2	331	70.35	23.33	192	67.11	19.93	<0.001***
Study Month 3	324	69.27	22.48	193	66.59	20.66	0.001**
Study Month 6	301	69.09	23.84	192	71.53[d]	57.03	
Study Month 12	260	67.60	23.16	187	66.44	18.99	
Study Month 18	227	67.69	23.94	177	66.01	19.83	
Study Month 24	187	66.34	24.41	137	66.59	22.94	
Study Month 30	112	64.04	22.83	80	64.06	26.80	
Study Month 36	79	63.62	23.01	53	64.78	27.21	
Study Month 42	53	60.89	22.01	37	68.06	28.77	
Study Month 48	23	58.03	26.68	20	68.97	30.92	
Study Month 54	6	68.55	29.06	11	80.63	38.08	
Study Month 60	6	72.85	36.19	9	85.65	44.32	
Study Month 66	1	74.30		3	117.13	57.04	

ANCOVA = analysis of covariance; CNI = calcineurin inhibitor; GFR = glomerular filtration rate; N = number of subjects with matching baseline; SRL = sirolimus; Std = standard deviation.

a. Statistical significance at the 0.05, 0.01, 0.001 levels is denoted by*, **, ***, respectively.
b. Comparisons between treatments are based on 1-way ANCOVA (unadjusted for multiplicity). The observed means in this table are arithmetic averages and not adjusted by the ANCOVA model used.
c. Baseline data.
d. Includes value of 805 for subject 313-003-001, which was based on a reported aberrant serum creatinine of 9 µmol/L.

Slope of Regression of Glomerular Filtration Rate

The annual change (slope) in the GFR using cumulative data was determined for On-Therapy and All-Visits data. The 6-month GFR data point for 1 subject (On-Therapy) appeared to be off by a factor of 10 and was suspected to have a misplaced decimal point. However, this could not be verified, so the analysis was run both with and without this single data point.

In the SRL conversion cohort there was a significant cumulative annual decrease in the GFR both in the On-Therapy analysis (-2.0 mL/min/yr; $p < 0.001$) and in the All-Visit analysis (-2.5 mL/min/yr; $p < 0.001$). This negative slope appears to reflect the loss over time of the significant increase in GFR which occurred in the SRL conversion cohort immediately after cessation of treatment with the CNI and initiation of therapy with SRL.

There was no significant cumulative change in the GFR in the CNI continuation cohort in the On-Therapy analysis (+0.1 mL/min/yr; $p=0.865$) or in the All-Visit analysis (-0.1 mL/min/yr; $p=0.870$).

Slope of Regression of 1/Creatinine

The, On-Therapy and All-Visits slopes were -0.00010 $(\mu mol/L)^{-1}$/year and 0.00018 $(\mu mol/L)^{-1}$/year respectively in the SRL continuation cohort, and 0.00002 $(\mu mol/L)^{-1}$/year and 0.00000 $(\mu mol/L)^{-1}$/year respectively in the CNI continuation group. The negative slope in the SRL cohort and the significant differences between the treatment groups reflect the erosion over time of the significant decrease in serum creatinine (and thus increase in 1/creatinine) which occurred in the SRL conversion cohort immediately after cessation of treatment with the CNI and initiation of therapy with SRL (see Table 11).

Serum Creatinine – On Therapy

Mean values for cumulative serum creatinine through month 66 for the On-Therapy population are presented in Table 11.

Table 11. Mean (±Std) Observed Creatinine (µmol/L): On Therapy

Time (After Randomization)	----SRL Conversion---- N	Mean	Std	----CNI Continuation---- N	Mean	Std	Between-Group p-Value[a, b]
Screening / Baseline[c]	389	123.3	29.7	210	124.7	29.8	
Day 28	357	114.8	38.6	200	123.8	30.8	<0.001[***d]
Study Month 2	333	113.9	32.8	195	122.7	31.5	<0.001[***d]
Study Month 3	326	115.0	33.4	196	123.6	32.1	<0.001[***d]
Study Month 6	303	117.0	39.0	195	120.9[e]	32.2	
Study Month 12	262	119.0	38.9	190	122.4	31.5	
Study Month 18	227	119.0	40.7	180	123.2	38.7	
Study Month 24	187	120.7	42.7	140	120.7	28.9	
Study Month 30	112	129.3	77.9	83	126.0	42.8	
Study Month 36	79	129.3	65.3	55	131.5	40.7	
Study Month 42	53	135.6	70.4	38	119.9	40.0	
Study Month 48	23	166.9	125.9	21	120.1	40.1	
Study Month 54	6	142.7	117.4	11	126.6	43.2	
Study Month 60	6	137.4	111.4	9	119.9	47.1	
Study Month 66	1	82.2		3	105.5	38.1	

ANCOVA = analysis of co-variance; CNI = calcineurin inhibitor; N = number of subjects with matching baseline; SRL = sirolimus; Std = standard deviation; vs versus.

a. Statistical significance at the 0.05, 0.01, 0.001 levels is denoted by*, **, ***, respectively.
b. Comparisons between treatments are based on 1-way ANCOVA (unadjusted for multiplicity). The observed means in this table are arithmetic averages and not adjusted by the ANCOVA model used.
c. Screening/baseline data.
d. SRL conversion vs CNI continuation.
e. Includes aberrant value of 9 µmol/L for one subject. Significant ($p \leq 0.05$) differences between groups are shown only if the overall comparison was significant.

Measured Glomerular Filtration Rate

Data on the change from Baseline in the measured GFR at Months 6, 12, 18, and 24, for the subset of subjects in whom the GFR was measured, are presented below in Table 12 and Table 13.

Table 12. Analysis of Directly Measured GFR: Change From Baseline Value Adjusted Means From ANCOVA Analysis by Treatment

Study Month	Group	Number of Subjects	Measured GFR Change From Baseline mL/min/BSA	Standard Error	95% CI: Lower Bound	95% CI: Upper Bound
Month 6	SRL Conversion	57	3.5	1.8	-0.1	7.2
	CNI Continuation	33	0.2	2.4	-4.5	5.0
Month 12	SRL Conversion	43	2.1	2.9	-3.7	7.8
	CNI Continuation	31	-3.7	3.4	-10.4	3.1
Month 18	SRL Conversion	39	1.0	2.3	-3.7	5.7
	CNI Continuation	30	0.2	2.7	-5.1	5.6
Month 24	SRL Conversion	38	1.8	2.4	-2.9	6.6
	CNI Continuation	24	-0.3	3.0	-6.3	5.8

ANCOVA with treatment as factor and baseline GFR as covariate.
ANCOVA = analysis of covariance; BSA = body surface area; CI = confidence interval; CNI = calcineurin inhibitor; GFR = glomerular filtration rate; SRL = sirolimus.

Table 13. Analysis of Directly Measured GFR: Change From Baseline Value Difference in Adjusted Means From ANCOVA Analysis of Directly Measured GFR

Study Month	(A)	(B)	Difference: (A) - (B)[a]	Standard Error	p-Value[b]	95% CI: Lower Bound	95% CI: Upper Bound
Month 6	SRL Conversion	CNI Continuation	3.3	3.0	0.274	-2.7	9.3
Month 12	SRL Conversion	CNI Continuation	5.7	4.4	0.200	-3.1	14.6
Month 18	SRL Conversion	CNI Continuation	0.8	3.6	0.824	-6.3	7.9
Month 24	SRL Conversion	CNI Continuation	2.1	3.8	0.585	-5.6	9.8

ANCOVA = analysis of covariance; CI = confidence interval; CNI = calcineurin inhibitor; GFR = glomerular filtration rate; SRL = sirolimus.

a. Differences >0 favor SRL continuation.

b. ANCOVA with treatment as factor and baseline GFR as covariate.

Failure to meet the primary efficacy endpoint (intent-to-treat [ITT] analysis of baseline-adjusted Cockroft-Gault glomerular filtration rate [GFR] at 12 months) led to early termination of the study. Because the study was terminated, the following planned analyses were not performed: Change from Baseline in measured GFR and Levey-calculated GFR; changes in liver histopathology (hepatic fibrosis score) and Quality of Life assessments. In addition, data for the endpoints, change from Baseline in mean systolic and diastolic blood pressure and mean arterial pressure for all subjects continuing with therapy at 12, 24, 36, 48, 60 and 72 months and change from Baseline in the antihypertensive agents administered at 12 and 24 months (ITT and On-Therapy populations) and in the percentage of subjects requiring treatment for hypertension were not reported. Because the study was terminated early, the only analyses done and reported in the final report were comparison of observed mean values of systolic, diastolic, and arterial blood pressure for the 2 treatment groups (SRL conversion and CNI continuation) using data up to month 12. Additional analyses included summaries of malignancy, serious infection and pneumonia, and stomatitis; supplementary efficacy analyses of the rate of the binary efficacy endpoint - rate of mean baseline-adjusted GFR; and analyses of subjects discontinued from randomized treatment with SRL (ie, subject survival after discontinuation from sirolimus, biopsy-confirmed rejection, serious infections). These analyses are on file, but are not included in this source report.

Because the study was terminated early owing to the failure to meet the primary study endpoints at month 12, the analyses of the post-12-month data were modified and reduced in number from those originally set out.

Safety Results:

Primary Safety Endpoint

The primary safety endpoint of the study was a composite of subject and graft survival at 12 months in the ITT population. A subject was considered to have reached this endpoint if either pure graft loss (with retransplant) or death with a functioning graft occurred within the first 12 months after random assignment to treatment. Subjects with missing survival data at the 12 month primary endpoint were counted as graft losses.)

As shown in Table 14 the overall rates for graft loss were 6.6% and 5.6% for the SRL conversion and CNI continuation cohorts, respectively. Based upon the Cochran-Mantel-Haenszel stratum weights (a function of sample size), the weighted difference in the rates of graft survival between treatments was -1.2% , with 95% CI [-5.2, 2.8]; the criterion for declaring non-inferiority was pre-specified as the lower bound of the 95% CI for the difference in rates of graft loss not being less than 5%. The study therefore failed to meet its primary safety endpoint of non-inferiority in rates of graft loss. The difference in rates of death in the SRL conversion and CNI continuation groups in a time to event analysis was not statistically significant (log rank p=0.170).

Table 14. Primary Analysis of Subject and Graft Survival (ITT Population)

Item	----------Study Treatment----------	
	SRL Conversion (N=393)	CNI Continuation (N=214)
Graft survival, n (%)	367 (93.4)	202 (94.4)
Graft loss, n (%)[a,b,c]	26 (6.6)	12 (5.6)
Weighted difference (95% confidence interval) in rates of graft loss[d,e]	-1.2 (-5.2, 2.8)	
Components of subject and graft survival,[f] (n (%)		
Death	13 (3.3)	3 (1.4)
Missing	13 (3.3)	9 (4.2)

CNI = calcineurin inhibitors; ITT = intent-to-treat; SRL = sirolimus.
a. Event rate is graft loss and death.
b. CMH p-Value for equality of treatments across strata: p=0.56 p-values <0.05 are significant.
c. Breslow-Day p-value tests for significant interactions between treatment and strata: p = 0.356.
d. Weighted difference in event rates (CNI - SRL%); negative values are favorable to CNI continuation.
e. Weighted 95% confidence interval for difference in event rates (CNI continuation - SRL conversion, percent).
f. No true graft losses (eg, liver transplants) were observed during the 12-month period.

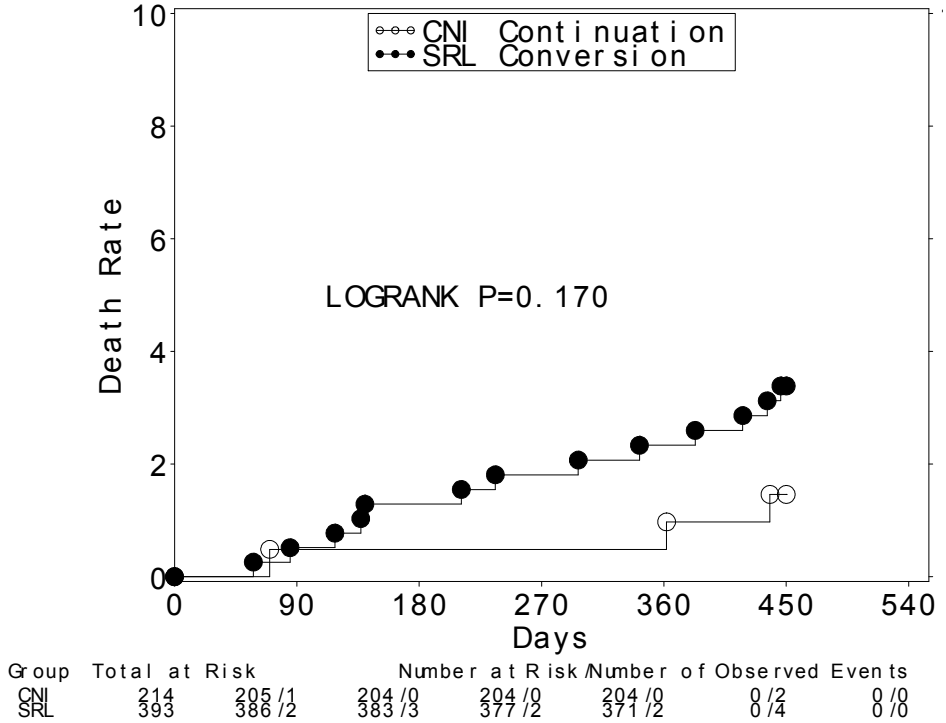
Secondary Safety Endpoints

Subject Survival

Because all of the subject and graft losses reported through Month 12 were due to subject deaths, the survival analysis provides no additional information beyond that available in Table 14.

A Kaplan-Meier plot of subject death rate through Month 12 is provided in Figure 2. (Note that this plot censors those missing subjects who were scored as events at the time of last visit in Table 14).

Figure 2. Incidence of Death Through Month 12 (ITT Population)



Deaths

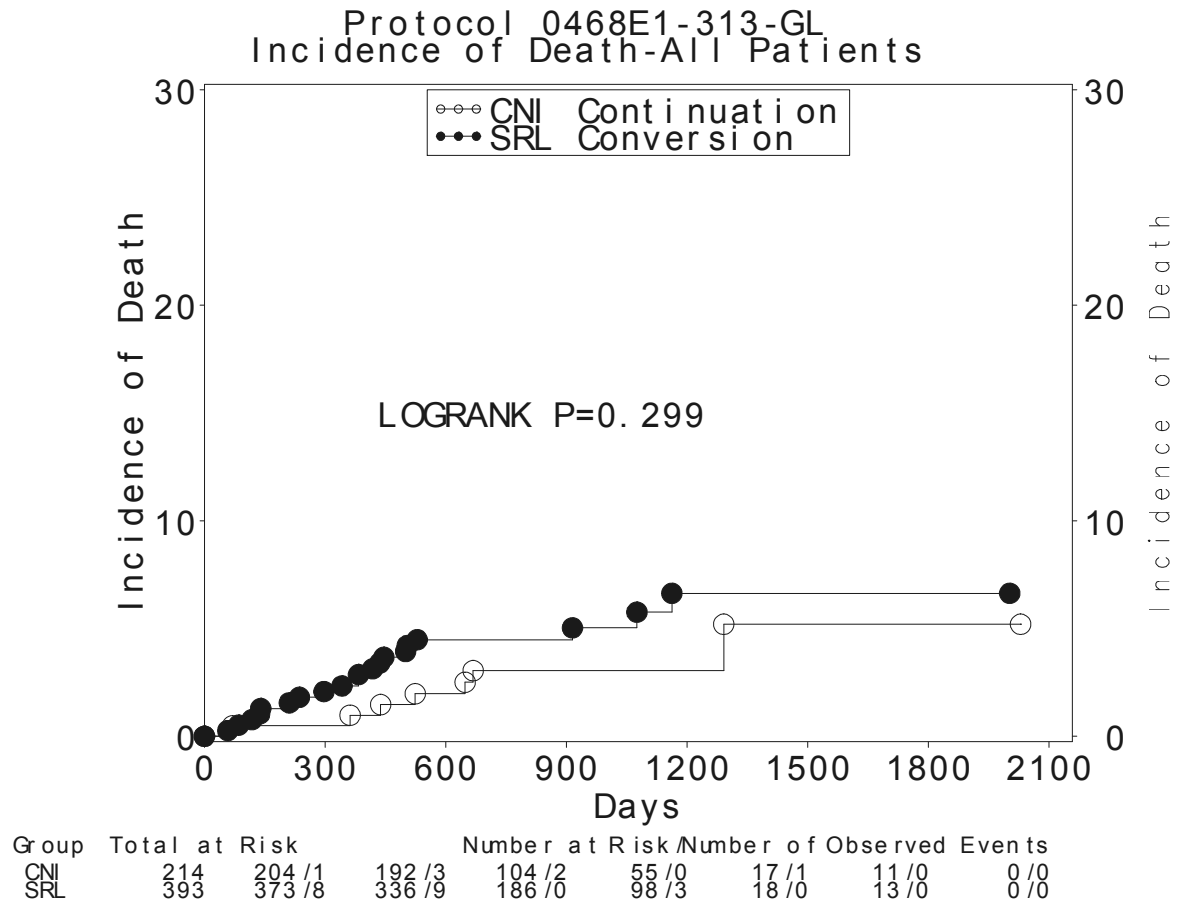
The cumulative number of deaths in each treatment group is presented in Table 15. Cumulative Kaplan-Meier rates of deaths are shown in Figure 3. Most deaths occurred during the first 2 years of the study. There was no significant difference between the 2 treatment groups. In the SRL conversion cohort, 8 of 20 deaths occurred in the first 300 days and 17 occurred in the first 600 days, with only 3 of 20 occurring thereafter. In the CNI conversion cohort, 1 of 7 deaths occurred in the first 300 days, 4 occurred in the first 600 days, and 3 of 7 occurred thereafter.

Table 15. Cumulative Number and Percentage of Deaths - All Subjects

	Study Treatment			
	SRL Conversion		CNI Continuation	
	n	%	n	%
N	393	(100.0)	214	(100.0)
Deaths	20	(5.1)	7	(3.3)
Survivors	373	(94.9)	207	(96.7)

Log-rank p-value (unstratified) is 0.299.
CNI = calcineurin inhibitor; N = total number of subjects; n = number of subjects in specified category; SRL = sirolimus.

Figure 3. Incidence of Death Through Month 72 (ITT Population)



CNI=calcineurin inhibitor; SRL=sirolimus.

Graft Loss and Deaths:

The cumulative numbers and percentages of graft losses are presented in Table 16. Cumulative Kaplan-Meier rates of graft loss and deaths are shown in Figure 4. All "graft losses" in the SRL conversion cohort and all but 1 in the CNI continuation cohort were the result of deaths. These data are similar to the data presented for deaths in the previous section. There was only 1 actual graft loss resulting in retransplantation; this case occurred in the CNI continuation cohort. As illustrated in the Kaplan-Meier plot below in Figure 4 .

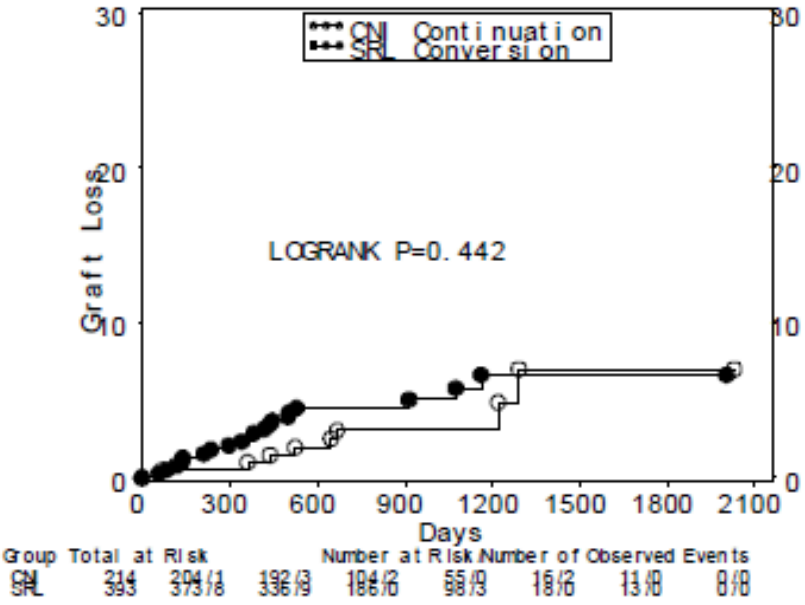
Table 16. Cumulative Graft Loss-All Subjects

	Study Treatment			
	SRL Conversion		CNI Continuation	
	n	%	n	%
N	393	(100.0)	214	(100.0)
Overall Event Rate				
Event	20	(5.1)	8	(3.7)
No Event	373	(94.9)	206	(96.3)
Type of endpoint				
Graft Loss	0	(0.0)	1	(0.5)
Death	20	(5.1)	7	(3.3)
No Event	373	(94.9)	206	(96.3)

Log-rank p-value (unstratified) is 0.442.
CNI=calcineurin inhibitor; N = total number of subjects; n = number of subjects in specified category
SRL=sirolimus..

As seen in Figure 4, in the SRL conversion cohort, 8 of a total of 20 graft loss events (all deaths) occurred in the first 300 days, 17 occurred in the first 600 days, with only 3 of 20 occurring thereafter. In the CNI conversion cohort 1 of 8 total graft-loss events occurred in the first 300 days, 4 occurred in the first 600 days, and 4 of 8 occurred thereafter.

Figure 4. Incidence of Graft Loss Through Month 72 (ITT Population)



Treatment Failure

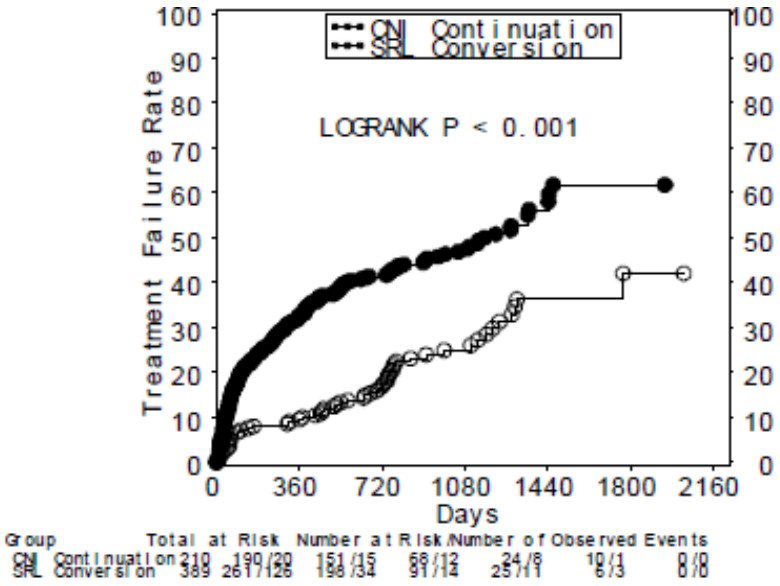
The cumulative instances of treatment failure (defined as the occurrence of acute rejection or premature discontinuation of study medication for any reason) for all subjects as of study end are reported in Table 17. Kaplan-Meier cumulative rates of treatment failure are presented in Figure 5.

Table 17. Sirolimus Treatment Failure

	Study Treatment			
	SRL Conversion		CNI Continuation	
	n	%	N	%
N	389	(100.0)	210	(100.0)
Overall Event Rate				
Yes	188	(48.3)	56	(26.7)
No	201	(51.7)	154	(73.3)
Type of endpoint				
Dose Termination	163	(41.9)	49	(23.3)
Acute Rejection	25	(6.4)	7	(3.3)
No Event	201	(51.7)	154	(73.3)

Log-rank p-value (unstratified) is < 0.001.
CNI = calcineurin inhibitor; N = total number of subjects; n = number of subjects in specified category; SRL = sirolimus

Figure 5. Incidence of Treatment Failure Through Month 72 (ITT Population)



Biopsy-Confirmed Acute Rejection: Cumulative Data

The overall rates of biopsy-confirmed acute rejection up to study end for the 2 treatment groups are presented in Table 18.

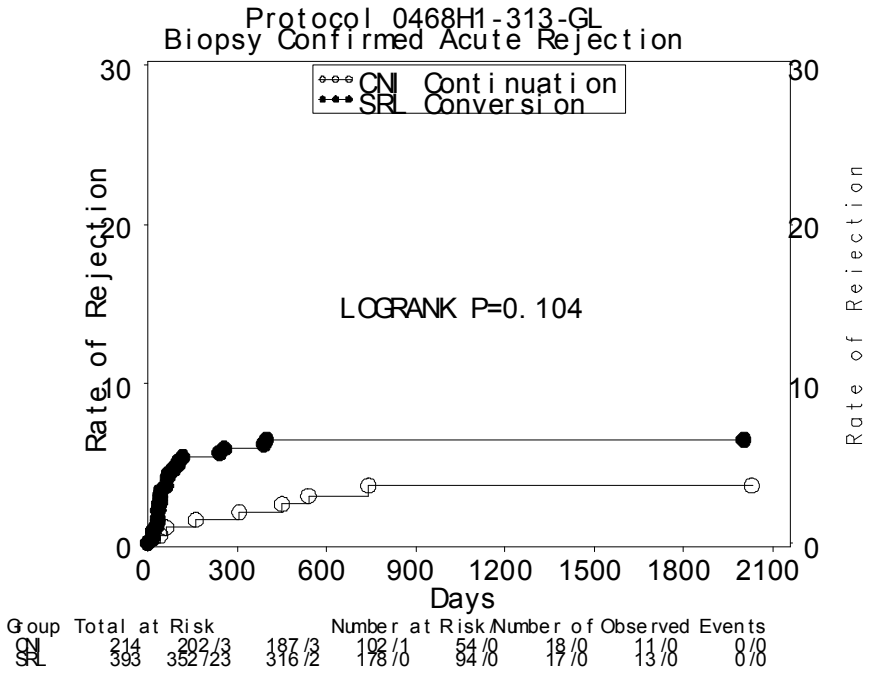
Table 18. Sirolimus Biopsy-Confirmed Acute Rejection

	Study Treatment			
	SRL Conversion		CNI Continuation	
	n	%	n	%
N	393	(100.0)	214	(100.0)
Acute Rejection	25	(6.4)	7	(3.3)

Log-rank p-value (unstratified) is 0.104.
CNI = calcineurin inhibitor; N = total number of subjects; n = number of subjects in specified category; SRL = sirolimus.

Cumulative Kaplan-Meier rates of biopsy-confirmed acute rejection are provided in Figure 6.

Figure 6. Incidence of Biopsy-Confirmed Acute Rejection Through Month 72 (ITT Population)



The distribution of biopsy-confirmed acute rejections by severity, as determined by the Banff diagnostic categories, is provided in Table 19.

Table 19. Distribution of Biopsy-Confirmed Acute Rejection Severity by Treatment

Study Treatment	Severity of Rejection								Total	
	None		Mild		Moderate		Severe			
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
SRL conversion	368	(93.6)	14	(3.6)	11	(2.8)	0	0	393	(100.0)
CNI continuation	207	(96.7)	4	(1.9)	2	(0.9)	1	(0.5)	214	(100.0)
Total	575	(94.7)	18	(3.0)	13	(2.1)	1	(0.2)	607	(100.0)

All severities are for reported rejections. CMH p-Value for row mean score test = 0.18.
CMH = Cochran-Mantel-Haenszel; CNI = calcineurin inhibitor; N = total number of subjects; SRL = sirolimus.

Adverse Events

For adverse events, it should be noted that due to changes in how the data were cut , differences in database (clinical trial data vs. ARGUS), differences in the type and version of the medical terminology dictionary used to describe events, as well as changes in the data programming (such as use of the treatment emergent algorithm, missing date imputation, drug lag), discrepancies may be evident when comparing the original adverse event data to that generated within the EU Results Disclosure tables of non-serious AEs, SAEs, and death (refers to tables Table 30, Table 31, Table 32, Table 33, and Table 34).

Most Common Treatment-Emergent Adverse Events

As is the case for all AEs, treatment-emergent adverse events (TEAEs) of malignancies and infections are reported separately. The rates of all nonmalignancy and noninfection TEAEs reported at a frequency of ≥5% through study end are presented in Table 20.

Table 20: Number (%) of Subjects Reporting TEAEs (Excluding Infection and Malignancy) That Occurred With an Incidence ≥5%

Body System[a] Adverse Event	Treatment SRL Conversion n=389 n(F)=120 n(M)=269	Treatment CNI Continuation n=210 n(F)=64 n(M)=146	Total n=599 n(F)=184 n(M)=415
Any adverse event	386 (99.2)	201 (95.7)	587 (98.0)
Body as a whole	280 (72.0)	135 (64.3)	415 (69.3)
Abdominal pain	70 (18.0)	30 (14.3)	100 (16.7)
Accidental injury	67 (17.2)	32 (15.2)	99 (16.5)
Asthenia	79 (20.3)	28 (13.3)	107 (17.9)
Back pain	42 (10.8)	27 (12.9)	69 (11.5)
Chest pain	34 (8.7)	21 (10.0)	55 (9.2)
Fever	79 (20.3)	26 (12.4)	105 (17.5)
Flu syndrome	24 (6.2)	8 (3.8)	32 (5.3)
Headache	84 (21.6)	23 (11.0)	107 (17.9)
Hernia	28 (7.2)	10 (4.8)	38 (6.3)
Pain	71 (18.3)	39 (18.6)	110 (18.4)
Cardiovascular system	131 (33.7)	80 (38.1)	211 (35.2)
Hypertension	65 (16.7)	40 (19.0)	105 (17.5)
Digestive system	317 (81.5)	114 (54.3)	431 (72.0)
Anorexia	25 (6.4)	6 (2.9)	31 (5.2)
Aphthous stomatitis	35 (9.0)	2 (1.0)	37 (6.2)
constipation	39 (10.0)	20 (9.5)	59 (9.8)
Diarrhea	136 (35.0)	38 (18.1)	174 (29.0)
dyspepsia	19 (4.9)	11 (5.2)	30 (5.0)
Gastrointestinal disorder	28 (7.2)	11 (5.2)	39 (6.5)
Liver function tests abnormal	59 (15.2)	25 (11.9)	84 (14.0)
Mouth ulceration	44 (11.3)	2 (1.0)	46 (7.7)
Nausea	51 (13.1)	19 (9.0)	70 (11.7)
Stomatitis	103 (26.5)	4 (1.9)	107 (17.9)
vomiting	37 (9.5)	21 (10.0)	58 (9.7)
Hemic and lymphatic system	175 (45.0)	45 (21.4)	220 (36.7)
Anemia	94 (24.2)	19 (9.0)	113 (18.9)
Leukopenia	55 (14.1)	10 (4.8)	65 (10.9)
Thrombocytopenia	58 (14.9)	8 (3.8)	66 (11.0)
Metabolic and nutritional	304 (78.1)	114 (54.3)	418 (69.8)
Creatinine increased	24 (6.2)	26 (12.4)	50 (8.3)
Hypercholesteremia	110 (28.3)	9 (4.3)	119 (19.9)
Hyperglycemia	39 (10.0)	22 (10.5)	61 (10.2)
Hyperlipemia	159 (40.9)	20 (9.5)	179 (29.9)
Peripheral edema	127 (32.6)	29 (13.8)	156 (26.0)
SGPT increased	40 (10.3)	9 (4.3)	49 (8.2)
Musculoskeletal system	114 (29.3)	56 (26.7)	170 (28.4)
Arthralgia	57 (14.7)	35 (16.7)	92 (15.4)
Nervous system	137 (35.2)	62 (29.5)	199 (33.2)
Respiratory system	159 (40.9)	61 (29.0)	220 (36.7)
Cough increased	66 (17.0)	28 (13.3)	94 (15.7)
Pharyngitis	40 (10.3)	14 (6.7)	54 (9.0)

Table 20: Number (%) of Subjects Reporting TEAEs (Excluding Infection and Malignancy) That Occurred With an Incidence ≥5%

Body System[a] Adverse Event	Treatment SRL Conversion n=389 n(F)=120 n(M)=269	Treatment CNI Continuation n=210 n(F)=64 n(M)=146	Total n=599 n(F)=184 n(M)=415
Skin and appendages	246 (63.2)	71 (33.8)	317 (52.9)
Acne	52 (13.4)	4 (1.9)	56 (9.3)
Pruritus	50 (12.9)	14 (6.7)	64 (10.7)
Rash	111 (28.5)	16 (7.6)	127 (21.2)
Special senses	63 (16.2)	27 (12.9)	90 (15.0)
Urogenital system	120 (30.8)	53 (25.2)	173 (28.9)
Kidney function abnormal	24 (6.2)	22 (10.5)	46 (7.7)
Adverse event associated with miscelaneous factors	51 (13.1)	22 (10.5)	73 (12.2)

For one subject event of 'Feeling of being cold' was mischaracterized in the 12-month report as an infection-related AE. In this cumulative study end report, the event is correctly reported as an AE.
AE = adverse event; CNI = calcineurin inhibitor; F = female; M = male; SGPT = serum glutamic pyruvic transaminase; SRL = sirolimus.
a. Body system totals are not necessarily the sum of the individual AEs because a subject may report 2 or more different AEs in the same body system.

Infections

The cumulative number and percentage of subjects with TEAEs of infection are presented in Table 21.

Table 21: Number (%) of Subjects Reporting TEAEs of Infection

Body System[a] Adverse Event	Sex[b]	Treatment SRL Conversion n=389 n(F)=120 n(M)=269	Treatment CNI Continuation n=210 n(F)=64 n(M)=146	Total n=599 n(F)=184 n(M)=415
Any adverse event		269 (69.2)	130 (61.9)	399 (66.6)
Body as a whole		141 (36.2)	66 (31.4)	207 (34.6)
Abdominal pain		0	1 (0.5)	1 (0.2)
Abdominal syndrome acute		0	1 (0.5)	1 (0.2)
Abscess		8 (2.1)	1 (0.5)	9 (1.5)
Accidental injury		1 (0.3)	1 (0.5)	2 (0.3)
Cellulitis		20 (5.1)	7 (3.3)	27 (4.5)
Chills		3 (0.8)	0	3 (0.5)
Cyst		2 (0.5)	0	2 (0.3)
Diarrhoea infectious		1 (0.3)	0	1 (0.2)
Fever		2 (0.5)	1 (0.5)	3 (0.5)
Flu syndrome		16 (4.1)	15 (7.1)	31 (5.2)
Infection		97 (24.9)	43 (20.5)	140 (23.4)
Infection superimposed		1 (0.3)	0	1 (0.2)
Moniliasis		0	1 (0.5)	1 (0.2)
Pain		2 (0.5)	0	2 (0.3)
Sepsis		11 (2.8)	5 (2.4)	16 (2.7)
Septic shock		1 (0.3)	0	1 (0.2)
Cardiovascular system		2 (0.5)	2 (1.0)	4 (0.7)
Pericarditis		0	1 (0.5)	1 (0.2)
Peripheral vascular disorder		1 (0.3)	0	1 (0.2)
Phlebitis		0	1 (0.5)	1 (0.2)
Thrombophlebitis		1 (0.3)	0	1 (0.2)
Digestive system		86 (22.1)	31 (14.8)	117 (19.5)
Aphthous stomatitis		11 (2.8)	1 (0.5)	12 (2.0)
Cheilitis		2 (0.5)	0	2 (0.3)
Cholangitis		4 (1.0)	0	4 (0.7)
Colitis		1 (0.3)	1 (0.5)	2 (0.3)
Diarrhea		6 (1.5)	4 (1.9)	10 (1.7)
Enteritis		0	1 (0.5)	1 (0.2)
Gastritis		0	1 (0.5)	1 (0.2)
Gastroenteritis		19 (4.9)	12 (5.7)	31 (5.2)
Gastrointestinal disorder		2 (0.5)	0	2 (0.3)
Gastrointestinal moniliasis		1 (0.3)	1 (0.5)	2 (0.3)
Gingivitis		2 (0.5)	1 (0.5)	3 (0.5)
Glossitis		1 (0.3)	0	1 (0.2)
Hepatitis		9 (2.3)	0	9 (1.5)
Mouth ulceration		7 (1.8)	1 (0.5)	8 (1.3)
Oral moniliasis		8 (2.1)	2 (1.0)	10 (1.7)
Periodontal abscess		8 (2.1)	5 (2.4)	13 (2.2)
Periodontitis		3 (0.8)	0	3 (0.5)
Rectal disorder		1 (0.3)	0	1 (0.2)
Stomatitis		18 (4.6)	5 (2.4)	23 (3.8)
Stools abnormal		1 (0.3)	0	1 (0.2)
Tooth disorder		1 (0.3)	0	1 (0.2)
Ulcerative stomatitis		2 (0.5)	0	2 (0.3)

Table 21: Number (%) of Subjects Reporting TEAEs of Infection

Body System[a] Adverse Event	Sex[b]	Treatment		
		SRL Conversion n=389 n(F)=120 n(M)=269	CNI Continuation n=210 n(F)=64 n(M)=146	Total n=599 n(F)=184 n(M)=415
Hemic and lymphatic system		2 (0.5)	0	2 (0.3)
Lymphadenopathy		1 (0.3)	0	1 (0.2)
Lymphangitis		1 (0.3)	0	1 (0.2)
Musculoskeletal system		0	2 (1.0)	2 (0.3)
Osteomyelitis		0	1 (0.5)	1 (0.2)
Tenosynovitis		0	1 (0.5)	1 (0.2)
Nervous system		1 (0.3)	1 (0.5)	2 (0.3)
dizziness		0	1 (0.5)	1 (0.2)
Neuropathic pain		1 (0.3)	0	1 (0.2)
Respiratory system		125 (32.1)	62 (29.5)	187 (31.2)
Aspiration pneumonia		0	1 (0.5)	1 (0.2)
Bronchiolitis		1 (0.3)	0	1 (0.2)
Bronchitis		25 (6.4)	14 (6.7)	39 (6.5)
Cough increased		1 (0.3)	0	1 (0.2)
Interstitial pneumonia		1 (0.3)	0	1 (0.2)
Laryngitis		4 (1.0)	2 (1.0)	6 (1.0)
Lung disorder		1 (0.3)	0	1 (0.2)
Pharyngitis		14 (3.6)	4 (1.9)	18 (3.0)
Pneumonia		30 (7.7)	9 (4.3)	39 (6.5)
Respiratory disorder		0	1 (0.5)	1 (0.2)
Rhinitis		4 (1.0)	1 (0.5)	5 (0.8)
Sinus congestion		0	1 (0.5)	1 (0.2)
Sinusitis		27 (6.9)	15 (7.1)	42 (7.0)
Upper respiratory infection		54 (13.9)	36 (17.1)	90 (15.0)
Skin and appendages		75 (19.3)	24 (11.4)	99 (16.5)
Contact dermatitis		1 (0.3)	1 (0.5)	2 (0.3)
Cutaneous moniliasis		1 (0.3)	0	1 (0.2)
Eczema		1 (0.3)	0	1 (0.2)
Exfoliative dermatitis		5 (1.3)	0	5 (0.8)
Folliculitis		6 (1.5)	1 (0.5)	7 (1.2)
Fungal dermatitis		18 (4.6)	6 (2.9)	24 (4.0)
Furunculosis		3 (0.8)	1 (0.5)	4 (0.7)
Herpes simplex		33 (8.5)	3 (1.4)	36 (6.0)
Herpes zoster		11 (2.8)	8 (3.8)	19 (3.2)
Impetigo		2 (0.5)	0	2 (0.3)
Nail disorder		1 (0.3)	0	1 (0.2)
Pruritus		1 (0.3)	0	1 (0.2)
Pustular rash		2 (0.5)	0	2 (0.3)
Rash		7 (1.8)	2 (1.0)	9 (1.5)
Seborrhea		1 (0.3)	0	1 (0.2)
Skin hypertrophy		0	1 (0.5)	1 (0.2)
Skin ulcer		1 (0.3)	1 (0.5)	2 (0.3)
Stasis dermatitis		1 (0.3)	0	1 (0.2)
Special senses		8 (2.1)	5 (2.4)	13 (2.2)
Conjunctivitis		5 (1.3)	2 (1.0)	7 (1.2)
Eye disorder		3 (0.8)	0	3 (0.5)
Otitis externa		0	1 (0.5)	1 (0.2)
Otitis media		2 (0.5)	2 (1.0)	4 (0.7)

Table 21: Number (%) of Subjects Reporting TEAEs of Infection

Body System[a] Adverse Event	Sex[b]	Treatment		
		SRL Conversion n=389 n(F)=120 n(M)=269	CNI Continuation n=210 n(F)=64 n(M)=146	Total n=599 n(F)=184 n(M)=415
Urogenital system		50 (12.9)	26 (12.4)	76 (12.7)
Cystitis		6 (1.5)	3 (1.4)	9 (1.5)
Dysuria		1 (0.3)	0	1 (0.2)
Kidney calculus		1 (0.3)	0	1 (0.2)
Orchitis	M	1 (0.4)	0	1 (0.2)
Prostatic disorder	M	2 (0.7)	0	2 (0.5)
Pyelonephritis		2 (0.5)	0	2 (0.3)
Urethritis		1 (0.3)	0	1 (0.2)
Urinary tract infection		36 (9.3)	21 (10.0)	57 (9.5)
Urination impaired		1 (0.3)	0	1 (0.2)
Vaginal moniliasis	F	1 (0.8)	2 (3.1)	3 (1.6)
Vaginitis	F	3 (2.5)	2 (3.1)	5 (2.7)
Terms not classifiable		1 (0.3)	0	1 (0.2)
Reaction unevaluable		1 (0.3)	0	1 (0.2)
Adverse event associated with miscellaneous factors		4 (1.0)	0	4 (0.7)
Local reaction to procedure		4 (1.0)	0	4 (0.7)

AE = adverse event; CNI = calcineurin inhibitor; CNS = central nervous system; F = female; M = male; N = total number of subjects in each treatment group; n = number of subjects in specified category; SRL = sirolimus; TEAEs = treatment emergent adverse events.

a. body system totals are not necessarily the sum of the individual AEs because a subject may report 2 or more different AEs in the same body system

b. F, M, or blank indicates the calculation is based on subjects of either female only, male only, or both.

Malignancies

The cumulative numbers and percentages of subjects with a TEAE of malignancy are presented in Table 22.

Table 22: Number (%) of Subjects Reporting TEAEs of Malignancy

Body System [a] Adverse Event	Sex[b]	Treatment: SRL Conversion n=389 n(M)=269	Treatment: CNI Continuation n=210 n(M)=146	Total n=599 n(M)=415
Any adverse event		47 (12.1)	36 (17.1)	83 (13.9)
Body as a whole		16 (4.1)	7 (3.3)	23 (3.8)
Carcinoma		2 (0.5)	0	2 (0.3)
Neoplasm		13 (3.3)	7 (3.3)	20 (3.3)
Ulcer		1 (0.3)	0	1 (0.2)
Digestive system		7 (1.8)	8 (3.8)	15 (2.5)
Carcinoma of mouth		0	1 (0.5)	1 (0.2)
Gastrointestinal carcinoma		4 (1.0)	4 (1.9)	8 (1.3)
Hepatic neoplasia		3 (0.8)	2 (1.0)	5 (0.8)
Mouth ulceration		0	1 (0.5)	1 (0.2)
Hemic and lymphatic system		1 (0.3)	0	1 (0.2)
Lymphadenopathy		1 (0.3)	0	1 (0.2)
Nervous system		0	1 (0.5)	1 (0.2)
CNS neoplasia		0	1 (0.5)	1 (0.2)
Respiratory system		4 (1.0)	2 (1.0)	6 (1.0)
Carcinoma of lung		3 (0.8)	2 (1.0)	5 (0.8)
Lung disorder		1 (0.3)	0	1 (0.2)
Skin and appendages		25 (6.4)	22 (10.5)	47 (7.8)
Erythema		0	1 (0.5)	1 (0.2)
Maculopapular rash		0	1 (0.5)	1 (0.2)
Skin benign neoplasm		10 (2.6)	5 (2.4)	15 (2.5)
Skin carcinoma		14 (3.6)	19 (9.0)	33 (5.5)
Skin hypertrophy		1 (0.3)	1 (0.5)	2 (0.3)
Skin melanoma		1 (0.3)	3 (1.4)	4 (0.7)
Urogenital system		4 (1.0)	1 (0.5)	5 (0.8)
Breast neoplasm		1 (0.3)	1 (0.5)	2 (0.3)
Prostatic carcinoma	M	3 (1.1)	0	3 (0.7)

AE = adverse event; CNI = calcineurin inhibitor; CNS = central nervous system; F = female; M = male; N = total number of subjects in each treatment group; n = number of subjects in specified category; SRL = sirolimus; TEAEs = treatment emergent adverse events.

a. body system totals are not necessarily the sum of the individual AEs because a subject may report 2 or more different AEs in the same body system

b. F, M, or blank indicates the calculation is based on subjects of either female only, male only, or both.

Stomatitis

Table 23 summarizes the cumulative rates of stomatitis at Month 72. The overall rate for stomatitis for the period was significantly higher in the SRL conversion cohort compared with the CNI continuation cohort (48.6% and 7.9%, respectively; p<0.001). Nearly all of these events occurred during the first 6 months after randomization (see Figure 7).

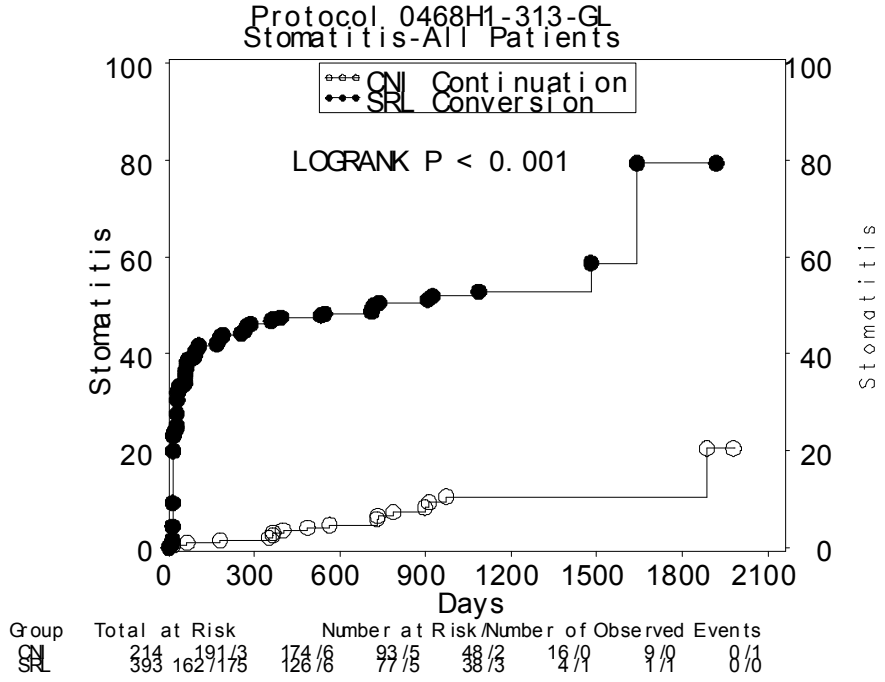
Table 23: Cumulative Rates of Stomatitis (Month 72)

	Study Treatment[a]			
	Sirolimus Conversion		CNI Continuation	
	n	%	n	%
N	393	(100.0)	214	(100.0)
Stomatitis	191	(48.6)	17	(7.9)
No Stomatitis	202	(51.4)	197	(92.1)

CNI = calcineurin inhibitor; N = total number of subjects in each treatment group; n = number of subjects in specified category.

a. Log-rank p-Value (unstratified) is <0.001.

Figure 7: Kaplan-Meier Plot of the First Event of Stomatitis for All Subjects at Month 72



Hepatitis C Viral RNA Concentrations

Baseline hepatitis C virus RNA concentration for those subjects who were stratified into the hepatitis C positive stratum through Month 24. Overall, hepatitis C virus RNA blood concentration was significantly lower in the sirolimus conversion cohort compared with the CNI continuation cohort at Month 3 (difference in adjusted means: -1.6 $\log_{10}$U/mL, 95% CI [-2.3, -0.9], $p<0.001$) but not at Months 6 or 12. At Month 3, but not at Months 6 or 12, the adjusted mean RNA titer of subjects with genotypes other than type 1 was significantly lower in the sirolimus conversion versus CNI continuation cohorts (difference in adjusted means: -3.4 $\log_{10}$U/mL, 95% CI [-4.7, -2.2], $p<0.001$). The adjusted mean RNA titers of subjects with genotype 1 infections were not significantly different between cohorts at Months 3, 6, or 12.

Because of the natural variation in hepatitis C virus RNA concentration in hepatitis C virus-infected subjects over time, the clinical significance of these differences, if any, is uncertain.

Safety-Related Discontinuations

Table 24 summarizes the TEAEs that were cited as reasons for prematurely withdrawing from the study up until study end.

Table 24: Number (%) of Subjects Reporting Treatment Emergent Adverse Events Causing Permanent Discontinuation of Test Article

Body System[a] Adverse Event	Treatment SRL Conversion n=389 n (F)=120[b]	Treatment CNI Continuation n=210 n (F)=64[b]	Total n=599 n (F)=184[b]
Any adverse event	126 (32.4)	24 (11.4)	150 (25.0)
Body as a whole	16 (4.1)	2 (1.0)	18 (3.0)
Abdominal pain	1 (0.3)	0	1 (0.2)
Abscess	1 (0.3)	0	1 (0.2)
Accidental injury	1 (0.3)	0	1 (0.2)
Allergic reaction	2 (0.5)	0	2 (0.3)
Asthenia	2 (0.5)	0	2 (0.3)
Carcinoma	1 (0.3)	0	1 (0.2)
Cellulitis	1 (0.3)	0	1 (0.2)
Chest pain	1 (0.3)	0	1 (0.2)
Drug level increased	0	1 (0.5)	1 (0.2)
Fever	1 (0.3)	0	1 (0.2)
Headache	1 (0.3)	0	1 (0.2)
Hernia	1 (0.3)	0	1 (0.2)
Infection	1 (0.3)	0	1 (0.2)
Neck pain	1 (0.3)	0	1 (0.2)
Overdose	1 (0.3)	0	1 (0.2)
Septic shock	1 (0.3)	0	1 (0.2)
Transplant rejection	0	1 (0.5)	1 (0.2)
Cardiovascular system	10 (2.6)	1 (0.5)	11 (1.8)
Angina pectoris	2 (0.5)	0	2 (0.3)
Aortic stenosis	1 (0.3)	0	1 (0.2)
Arterial thrombosis	2 (0.5)	0	2 (0.3)
Cardiovascular disorder	1 (0.3)	0	1 (0.2)
Heart failure	1 (0.3)	0	1 (0.2)
Mesenteric venous occlusion	1 (0.3)	0	1 (0.2)
Pericardial effusion	1 (0.3)	0	1 (0.2)
Pulmonary embolus	0	1 (0.5)	1 (0.2)
Shock	1 (0.3)	0	1 (0.2)
Syncope	1 (0.3)	0	1 (0.2)
Digestive system	34 (8.7)	4 (1.9)	38 (6.3)
Abdominal distension	1 (0.3)	0	1 (0.2)
Aphthous stomatitis	2 (0.5)	0	2 (0.3)
Diarrhea	4 (1.0)	0	4 (0.7)
Esophagitis	1 (0.3)	0	1 (0.2)
Gamma glutamyl transpeptidase increased	1 (0.3)	0	1 (0.2)
Gastroenteritis	1 (0.3)	0	1 (0.2)
Gastrointestinal carcinoma	1 (0.3)	2 (1.0)	3 (0.5)
Gastrointestinal disorder	2 (0.5)	0	2 (0.3)
Gastrointestinal hemorrhage	1 (0.3)	0	1 (0.2)
Hepatic neoplasia	1 (0.3)	1 (0.5)	2 (0.3)
Hepatitis	2 (0.5)	0	2 (0.3)
Liver damage	1 (0.3)	0	1 (0.2)
Liver function tests abnormal	2 (0.5)	1 (0.5)	3 (0.5)
Mouth ulceration	5 (1.3)	0	5 (0.8)
Nausea	1 (0.3)	0	1 (0.2)
Rectal disorder	1 (0.3)	0	1 (0.2)
Stomatitis	7 (1.8)	0	7 (1.2)

Table 24: Number (%) of Subjects Reporting Treatment Emergent Adverse Events Causing Permanent Discontinuation of Test Article

Body System[a] Adverse Event	Treatment SRL Conversion n=389 n (F)=120[b]	Treatment CNI Continuation n=210 n (F)=64[b]	Total n=599 n (F)=184[b]
Endocrine system	1 (0.3)	0	1 (0.2)
Diabetes mellitus	1 (0.3)	0	1 (0.2)
Hemic and lymphatic system	7 (1.8)	1 (0.5)	8 (1.3)
Anemia	2 (0.5)	0	2 (0.3)
Leukopenia	3 (0.8)	0	3 (0.5)
Microcytic anemia	1 (0.3)	0	1 (0.2)
Pancytopenia	1 (0.3)	1 (0.5)	2 (0.3)
Metabolic and nutritional	21 (5.4)	4 (1.9)	25 (4.2)
Creatinine increased	0	4 (1.9)	4 (0.7)
Edema	3 (0.8)	0	3 (0.5)
Healing abnormal	2 (0.5)	0	2 (0.3)
Hypercholesteremia	1 (0.3)	0	1 (0.2)
Hyperglycemia	1 (0.3)	0	1 (0.2)
Hyperlipemia	1 (0.3)	0	1 (0.2)
Peripheral edema	13 (3.3)	0	13 (2.2)
Musculoskeletal system	3 (0.8)	0	3 (0.5)
Arthralgia	1 (0.3)	0	1 (0.2)
Arthritis	1 (0.3)	0	1 (0.2)
Musculoskeletal anomaly	1 (0.3)	0	1 (0.2)
Nervous system	1 (0.3)	1 (0.5)	2 (0.3)
Emotional lability	1 (0.3)	0	1 (0.2)
Hyperesthesia	0	1 (0.5)	1 (0.2)
Respiratory system	11 (2.8)	1 (0.5)	12 (2.0)
Carcinoma of lung	1 (0.3)	1 (0.5)	2 (0.3)
Cough increased	1 (0.3)	0	1 (0.2)
Lung disorder	1 (0.3)	0	1 (0.2)
Lung edema	1 (0.3)	0	1 (0.2)
Pneumonia	2 (0.5)	0	2 (0.3)
Pneumonitis	4 (1.0)	0	4 (0.7)
Upper respiratory infection	1 (0.3)	0	1 (0.2)
Skin and appendages	16 (4.1)	1 (0.5)	17 (2.8)
Acne	2 (0.5)	0	2 (0.3)
Angioedema	1 (0.3)	0	1 (0.2)
Eczema	2 (0.5)	0	2 (0.3)
Folliculitis	1 (0.3)	0	1 (0.2)
Maculopapular rash	1 (0.3)	0	1 (0.2)
Rash	6 (1.5)	0	6 (1.0)
Skin carcinoma	1 (0.3)	0	1 (0.2)
Skin disorder	1 (0.3)	0	1 (0.2)
Skin melanoma	0	1 (0.5)	1 (0.2)
Urticaria	2 (0.5)	0	2 (0.3)
Special senses	1 (0.3)	0	1 (0.2)
Ear disorder	1 (0.3)	0	1 (0.2)

Table 24: Number (%) of Subjects Reporting Treatment Emergent Adverse Events Causing Permanent Discontinuation of Test Article

Body System[a] Adverse Event	Treatment SRL Conversion n=389 n (F)=120[b]	Treatment CNI Continuation n=210 n (F)=64[b]	Total n=599 n (F)=184[b]
Urogenital system	9 (2.3)	9 (4.3)	18 (3.0)
Albuminuria	2 (0.5)	0	2 (0.3)
Kidney failure	2 (0.5)	1 (0.5)	3 (0.5)
Kidney function abnormal	3 (0.8)	6 (2.9)	9 (1.5)
Nephrosclerosis	1 (0.3)	0	1 (0.2)
Unintended pregnancy (F)[b]	0	1 (1.6)	1 (0.5)
Uremia	0	1 (0.5)	1 (0.2)
Vulvovaginal disorder (F)[b]	1 (0.8)	0	1 (0.5)

AE = adverse event; CNI = calcineurin inhibitor; F = female; M = male; N = total number of subjects in each treatment group; n = number of subjects in specified category; SRL = sirolimus.
a. Body system totals are not necessarily the sum of the individual AEs because a subject may report 2 or more different AEs in the same body system.
b. (F) indicates the calculation was based on female subjects only.

Deaths

Table 25 provides a tabulation of deaths by cause of death.

Table 25: Number and Percentage of Deaths by Cause

	Sirolimus Conversion	% of Total Sirolimus Conversion Enrolled	CNI Continuation	% of Total CNI Continuation Enrolled
Total enrolled to treatment group	389	100 %	210	100 %
Total deaths	20	5.14 %	7	3.33 %
Deaths from malignancy	9	2.31 %	5	2.38 %
Deaths from non-malignancy causes	11	2.83 %	2	0.95 %
Infection	4	1.03 %	0	0.00 %
Noninfection	7	1.80 %	2	0.95 %

CNI = calcineurin inhibitor.

A listing of individual subjects who died during the study is presented in Table 26.

Table 26: Subjects Who Died and Causes of Death

Subject	Study Day	Cause Of Death	Relationship
SRL Conversion Treatment (n=20)			
1	27	Skin carcinoma	Probably not
2	105	Lymphoma	Definitely not
3	1020	Gastrointestinal carcinoma	Probably not
4	865	Skin melanoma	Possibly
5	58	Sepsis	Probably
6	236	Accidental injury	Definitely not
7	833	Hepatic neoplasia	Possibly
8	49	Carcinoma	Definitely not
9	297	Gastrointestinal carcinoma	Definitely not
10	335	Shock	Definitely not
11	411	Sepsis	Probably not
12	285	Carcinoma	Probably not
13	529	Myocardial infarct	Possibly
14	82	Pneumonia	Probably
15	428	Liver damage	Probably not
16	196	Cerebrovascular accident	Definitely not
17	190	Carcinoma	Definitely not
18	383	Death	Definitely not
19	504	Gastrointestinal hemorrhage	Probably not
20	444	Septic shock	Probably
21[a]	332	Carcinoma of lung	Not related
CNI Continuation Treatment (n=7)			
22	362	Gastrointestinal carcinoma	Possibly
23	345	Carcinoma of lung	Probably not
24	492	Gastrointestinal carcinoma	Probably not
25	1291	Carcinoma of larynx	Definitely not
26	356	Skin melanoma	Probably
27	639	Pulmonary embolus	Definitely not
28	43	Aplastic anemia	Definitely not

CNI = calcineurin inhibitor; SRL = sirolimus.

a. Subject terminated participation in the study before death, and thus by protocol, this death should not have been reported. However, it is included for completeness and is not included in any analyses of subject death or the subject and graft survival combined primary safety endpoint.

Malignancy

A listing of first reported malignancies in each cohort during the study for the SRL conversion and CNI continuation cohorts are presented in Table 27 and Table 28.

Table 27: Listing of First Reported Malignancies Treatment: SRL Conversion

Subject	Preferred Term	Study Day of Malignancy Diagnosis	Treatment Emergent?
1	Skin carcinoma	409	Yes
2	Skin carcinoma	211	Yes
3	Skin carcinoma	9	Yes
4	Skin benign neoplasm	1093	Yes
5	Prostatic carcinoma	485	Yes
6	Lymphoma	105	No
7	Skin carcinoma	-1	No
8	Neoplasm	44	Yes
9	Gastrointestinal carcinoma	1020	Yes
10	Carcinoma of larynx	429	No
11	Skin carcinoma	1604	Yes
12	Skin melanoma	81	Yes
13	Neoplasm	124	Yes
14	Skin carcinoma	1142	Yes
15	Skin benign neoplasm	131	Yes
16	Skin carcinoma	-4	No
17	Neoplasm	149	Yes
18	Skin benign neoplasm	32	Yes
19	Skin carcinoma	173	Yes
20	Skin carcinoma	-15	No
21	Carcinoma	49	Yes
22	Neoplasm	363	Yes
23	Skin carcinoma	545	Yes
24	Gastrointestinal carcinoma	297	No
25	Prostatic carcinoma	209	Yes
26	Skin carcinoma	338	No
27	Hepatic neoplasia	337	Yes
28	Skin carcinoma	159	Yes
29	Skin carcinoma	331	Yes
30	Neoplasm	51	Yes
31	Gastrointestinal carcinoma	112	Yes
32	Carcinoma	285	No
33	Hepatic neoplasia	942	Yes
34	Skin carcinoma	963	No
35	Skin carcinoma	44	Yes
36	Gastrointestinal carcinoma	1250	Yes
37	Skin benign neoplasm	382	Yes
38	Neoplasm	601	Yes
39	Skin disorder	533	No
40	Skin carcinoma	1357	No
41	Breast neoplasm	1128	Yes
42	Skin carcinoma	364	No
43	Neoplasm	92	Yes
44	Prostatic carcinoma	965	Yes
45	Bladder neoplasm	161	No
46	Ulcer	914	Yes
47	Carcinoma of lung	661	No
48	Skin benign neoplasm	188	Yes
49	Skin carcinoma	688	No
49	Bladder carcinoma	117	No
50	Skin carcinoma	31	Yes
51	Skin carcinoma	255	Yes

Table 27: Listing of First Reported Malignancies Treatment: SRL Conversion

Subject	Preferred Term	Study Day of Malignancy Diagnosis	Treatment Emergent?
52	Prostatic carcinoma	720	No
53	Gastrointestinal carcinoma	435	Yes
54	Skin benign neoplasm	154	Yes
55	Neoplasm	427	Yes
56	Skin benign neoplasm	-5005	No
57	Skin carcinoma	178	Yes
58	Skin carcinoma	-230	No
59	Skin benign neoplasm	547	Yes
60	Carcinoma of lung	197	Yes
61	Carcinoma of lung	755	Yes
62	Neoplasm	619	Yes
63	Neoplasm	209	Yes
64	Skin carcinoma	736	Yes
65	Neoplasm	698	Yes

SRL = sirolimus.

Table 28: Listing of First Reported Malignancies Treatment: CNI Continuation

Subject	Preferred Term	Study Day of Malignancy Diagnosis	Treatment Emergent?
1	Skin carcinoma	1214	Yes
2	Skin carcinoma	62	Yes
3	Skin carcinoma	504	Yes
4	Skin benign neoplasm	1194	Yes
5	Skin carcinoma	296	Yes
6	Neoplasm	170	Yes
7	Skin carcinoma	425	Yes
8	Hepatic neoplasia	769	Yes
9	Skin carcinoma	555	Yes
10	Neoplasm	506	Yes
11	Skin carcinoma	76	Yes
12	Carcinoma of mouth	281	Yes
13	Skin benign neoplasm	91	Yes
14	Gastrointestinal carcinoma	484	Yes
15	Skin carcinoma	406	Yes
16	Neoplasm	-490	No
17	Skin carcinoma	104	Yes
18	Skin benign neoplasm	572	Yes
19	Skin carcinoma	27	Yes
20	Skin carcinoma	247	Yes
21	Skin carcinoma	189	Yes
22	Skin carcinoma	525	Yes
23	Carcinoma of larynx	1291	No
24	Skin benign neoplasm	403	Yes
25	Skin carcinoma	1367	No
26	Breast neoplasm	263	Yes
27	Neoplasm	477	Yes
28	Skin melanoma	356	Yes
29	CNS neoplasia	495	Yes
30	Neoplasm	1049	Yes
31	Skin carcinoma	812	Yes
32	Neoplasm	822	Yes
33	Gastrointestinal carcinoma	473	Yes
34	Gastrointestinal carcinoma	27	Yes
35	Neoplasm	64	Yes
36	Skin carcinoma	671	Yes
37	Skin melanoma	860	Yes
38	Maculopapular rash	60	Yes
39	Hepatic neoplasia	85	Yes

CNI = calcineurin inhibitor.

Other Life-Threatening Adverse Events

Nonfatal, nonmalignancy-related, life-threatening events are listed in Table 29.

Table 29: Listing of Nonfatal Nonmalignancy-Related Life-Threatening TEAEs – Final Cumulative Data

Subject	Study Day At Onset	Event	Outcome
SRL Conversion Treatment (n=7)			
1	669	Subdural hematoma	Resolved
2	323	Cholangitis	Resolved
3	323	Gastrointestinal disorder	Resolved
4	701	AV block complete	Resolved
5	260	Sepsis	Resolved
6	320	Healing abnormal	Resolved
7	90	Hemothorax	Resolved
8	444	Pneumonia	Persisted
CNI Continuation Treatment (n=3)			
9	1025	Cholangitis	Resolved
10	1062	Depression	Resolved
11	1384	Anemia	Persisted
12	715	AV block complete	Resolved

AV = atrioventricular; CNI = calcineurin inhibitor; n = number of subjects in specified category; SRL = sirolimus; TEAEs = treatment-emergent adverse events.

Treatment-emergent non serious adverse events by system organ class and preferred term (all causalities) in ≥5% of subjects is presented in Table 30.

Table 30: Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in ≥5 % of Subjects

	Cyclosporine / Tacrolimus		Sirolimus Conc Control	
Number of Subjects Evaluable for AEs:	**210**		**389**	
Number (%) of Subjects With AEs	**180**	**(88.6)**	**375**	**(96.4)**
Number (%) of Subjects with AEs by:	**N**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Blood and lymphatic system disorders	21	(10.0)	119	(30.6)
Anaemia	14	(6.7)	78	(20.1)
Leukopenia	6	(2.9)	45	(11.6)
Thrombocytopenia	5	(2.4)	45	(11.6)
Gastrointestinal disorders	81	(38.6)	269	(69.2)
Abdominal pain	16	(7.6)	39	(10.0)
Aphthous stomatitis	3	(1.4)	48	(12.3)
Constipation	20	(9.5)	36	(9.3)
Diarrhoea	39	(18.6)	129	(33.2)
Mouth ulceration	3	(1.4)	43	(11.1)
Nausea	19	(9.0)	47	(12.1)
Stomatitis	11	(5.2)	113	(29.0)
Vomiting	16	(7.6)	31	(8.0)
General disorders and administration site conditions	64	(30.5)	204	(52.4)
Asthenia	14	(6.7)	26	(6.7)
Fatigue	17	(8.1)	60	(15.4)
Oedema peripheral	27	(12.9)	124	(31.9)
Pain	12	(5.7)	16	(4.1)
Pyrexia	22	(10.5)	73	(18.8)
Infections and infestations	65	(40.5)	173	(44.5)
Bronchitis	12	(5.7)	24	(6.2)
Influenza	17	(8.1)	26	(6.7)
Nasopharyngitis	24	(11.4)	57	(14.7)
Oral herpes	1	(0.5)	22	(5.7)
Sinusitis	15	(7.1)	24	(6.2)
Upper respiratory tract infection	35	(16.7)	51	(13.1)
Urinary tract infection	18	(8.6)	32	(8.2)
Investigations	59	(28.1)	150	(38.6)
Alanine aminotransferase increased	9	(4.3)	40	(10.3)
Aspartate aminotransferase increased	12	(5.7)	35	(9.0)
Blood alkaline phosphatase increased	10	(4.8)	32	(8.2)
Blood cholesterol increased	2	(1.0)	31	(8.0)
Blood creatinine increased	24	(11.4)	22	(5.7)
Blood lactate dehydrogenase increased	3	(1.4)	20	(5.1)
Blood triglycerides increased	7	(3.3)	35	(9.0)
Blood urea increased	12	(5.7)	11	(2.8)
Liver function test abnormal	16	(7.6)	39	(10.0)
Weight decreased	6	(2.9)	26	(6.7)
Metabolism and nutrition disorders	48	(22.9)	186	(47.8)
Decreased appetite	5	(2.4)	25	(6.4)
Diabetes mellitus	7	(3.3)	20	(5.1)
Hypercholesterolaemia	7	(3.3)	76	(19.5)
Hyperglycaemia	15	(7.1)	25	(6.4)
Hyperkalaemia	12	(5.7)	7	(1.8)
Hyperlipidaemia	6	(2.9)	59	(15.2)
Hypertriglyceridaemia	7	(3.3)	61	(15.7)
Hypokalaemia	4	(1.9)	20	(5.1)

Table 30: Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in ≥5 % of Subjects

	Cyclosporine / Tacrolimus		Sirolimus Conc Control	
Number of Subjects Evaluable for AEs:	**210**		**389**	
Number (%) of Subjects With AEs	**180**	**(88.6)**	**375**	**(96.4)**
Number (%) of Subjects with AEs by:	**N**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Musculoskeletal and connective tissue disorders	68	(32.4)	117	(30.1)
Arthralgia	34	(16.2)	57	(14.7)
Back pain	26	(12.4)	40	(10.3)
Muscle spasms	15	(7.1)	14	(3.6)
Pain in extremity	22	(10.5)	41	(10.5)
Nervous system disorders	33	(15.7)	105	(27.0)
Dizziness	15	(7.1)	37	(9.5)
Headache	21	(10.0)	82	(21.1)
Psychiatric disorders	21	(10.0)	48	(12.3)
Depression	12	(5.7)	16	(4.1)
Insomnia	11	(5.2)	34	(8.7)
Renal and urinary disorders	16	(7.6)	33	(8.5)
Proteinuria	5	(2.4)	24	(6.2)
Renal impairment	13	(6.2)	11	(2.8)
Respiratory, thoracic and mediastinal disorders	38	(18.1)	102	(26.2)
Cough	26	(12.4)	60	(15.4)
Dyspnoea	9	(4.3)	29	(7.5)
Oropharyngeal pain	13	(6.2)	39	(10.0)
Skin and subcutaneous tissue disorders	36	(17.1)	180	(46.3)
Acne	4	(1.9)	49	(12.6)
Dry skin	2	(1.0)	29	(7.5)
Erythema	4	(1.9)	25	(6.4)
Pruritus	15	(7.1)	49	(12.6)
Rash	14	(6.7)	93	(23.9)
Vascular disorders	36	(17.1)	55	(14.1)
Hypertension	36	(17.1)	55	(14.1)

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (v15.0) coding dictionary applied.

Treatment-emergent non serious adverse events by system organ class and preferred term (all causalities) in >5% of subjects is presented in Table 31.

Table 31: Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5% of Subjects

	Cyclosporine/Tacrolimus				Sirolimus Concentration Control			
Number of Subjects Evaluable for AEs	**210**				**389**			
Number (%) of Subjects With AEs	**186**	**(88.6)**			**375**	**(96.4)**		
Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Blood and lymphatic system disorders	21	(10.0)	52	3	119	(30.6)	425	372
Anaemia	14	(6.7)	26	1	78	(20.1)	186	161
Leukopenia	6	(2.9)	17	0	45	(11.6)	129	116
Thrombocytopenia	5	(2.4)	9	2	45	(11.6)	110	95
Gastrointestinal disorders	81	(38.6)	224	15	269	(69.2)	1238	846
Abdominal pain	16	(7.6)	36	2	39	(10.0)	77	10
Aphthous stomatitis	3	(1.4)	3	1	48	(12.3)	129	118
Constipation	20	(9.5)	28	0	36	(9.3)	67	22
Diarrhoea	39	(18.6)	77	3	129	(33.2)	282	129
Mouth ulceration	3	(1.4)	4	3	43	(11.1)	109	101
Nausea	19	(9.0)	35	3	47	(12.1)	72	26
Stomatitis	11	(5.2)	23	2	113	(29.0)	454	428
Vomiting	16	(7.6)	18	1	31	(8.0)	48	12
General disorders and administration site conditions	64	(30.5)	170	15	204	(52.4)	664	290
Asthenia	14	(6.7)	26	2	26	(6.7)	48	17
Fatigue	17	(8.1)	32	0	60	(15.4)	97	41
Oedema peripheral	27	(12.9)	67	10	124	(31.9)	365	199
Pain	12	(5.7)	18	2	16	(4.1)	25	6
Pyrexia	22	(10.5)	27	1	73	(18.8)	129	27
Infections and infestations	85	(40.5)	228	37	173	(44.5)	478	145
Bronchitis	12	(5.7)	14	2	24	(6.2)	42	11
Influenza	17	(8.1)	30	4	26	(6.7)	40	4
Nasopharyngitis	24	(11.4)	51	10	57	(14.7)	122	42
Oral herpes	1	(0.5)	1	0	22	(5.7)	45	28
Sinusitis	15	(7.1)	29	11	24	(6.2)	42	13
Upper respiratory tract infection	35	(16.7)	74	3	51	(13.1)	138	30
Urinary tract infection	18	(8.6)	29	7	32	(8.2)	49	17
Investigations	59	(28.1)	210	92	150	(38.6)	654	440
Alanine aminotransferase increased	9	(4.3)	19	8	40	(10.3)	90	52
Aspartate aminotransferase increased	12	(5.7)	25	6	35	(9.0)	84	46
Blood alkaline phosphatase increased	10	(4.8)	22	5	32	(8.2)	88	54
Blood cholesterol increased	2	(1.0)	4	2	31	(8.0)	61	59
Blood creatinine increased	24	(11.4)	42	31	22	(5.7)	42	21
Blood lactate dehydrogenase increased	3	(1.4)	5	3	20	(5.1)	58	52
Blood triglycerides increased	7	(3.3)	20	8	35	(9.0)	75	72
Blood urea increased	12	(5.7)	28	17	11	(2.8)	24	18
Liver function test abnormal	16	(7.6)	36	12	39	(10.0)	83	55
Weight decreased	6	(2.9)	9	0	26	(6.7)	49	11
Metabolism and nutrition disorders	48	(22.9)	130	64	186	(47.8)	646	522
Decreased appetite	5	(2.4)	8	0	25	(6.4)	46	22
Diabetes mellitus	7	(3.3)	10	4	20	(5.1)	36	16
Hypercholesterolaemia	7	(3.3)	14	9	76	(19.5)	190	189
Hyperglycaemia	15	(7.1)	33	15	25	(6.4)	60	24
Hyperkalaemia	12	(5.7)	24	19	7	(1.8)	10	3
Hyperlipidaemia	6	(2.9)	11	3	59	(15.2)	99	94
Hypertriglyceridaemia	7	(3.3)	20	14	61	(15.7)	171	165
Hypokalaemia	4	(1.9)	10	0	20	(5.1)	34	9

Table 31: Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5% of Subjects

	Cyclosporine/Tacrolimus				Sirolimus Concentration Control			
Number of Subjects Evaluable for AEs	**210**				**389**			
Number (%) of Subjects With AEs	**186**	**(88.6)**			**375**	**(96.4)**		
Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Musculoskeletal and connective tissue disorders	68	(32.4)	198	5	117	(30.1)	337	68
Arthralgia	34	(16.2)	86	0	57	(14.7)	152	39
Back pain	26	(12.4)	42	0	40	(10.3)	80	3
Muscle spasms	15	(7.1)	33	5	14	(3.6)	27	1
Pain in extremity	22	(10.5)	37	0	41	(10.5)	78	25
Nervous system disorders	33	(15.7)	82	5	105	(27.0)	207	60
Dizziness	15	(7.1)	26	0	37	(9.5)	48	8
Headache	21	(10.0)	56	5	82	(21.1)	159	52
Psychiatric disorders	21	(10.0)	44	4	48	(12.3)	85	20
Depression	12	(5.7)	28	2	16	(4.1)	27	3
Insomnia	11	(5.2)	16	2	34	(8.7)	58	17
Renal and urinary disorders	16	(7.6)	37	34	33	(8.5)	75	57
Proteinuria	5	(2.4)	9	8	24	(6.2)	45	37
Renal impairment	13	(6.2)	28	26	11	(2.8)	30	20
Respiratory, thoracic and mediastinal disorders	38	(18.1)	78	2	102	(26.2)	267	66
Cough	26	(12.4)	48	1	60	(15.4)	139	32
Dyspnoea	9	(4.3)	12	0	29	(7.5)	56	18
Oropharyngeal pain	13	(6.2)	18	1	39	(10.0)	72	16
Skin and subcutaneous tissue disorders	36	(17.1)	75	14	180	(46.3)	629	428
Acne	4	(1.9)	7	3	49	(12.6)	145	102
Dry skin	2	(1.0)	4	1	29	(7.5)	64	42
Erythema	4	(1.9)	7	0	25	(6.4)	53	36
Pruritus	15	(7.1)	32	6	49	(12.6)	110	55
Rash	14	(6.7)	25	4	93	(23.9)	257	193
Vascular disorders	36	(17.1)	57	40	55	(14.1)	86	36
Hypertension	36	(17.1)	57	40	55	(14.1)	86	36

Subjects are only counted once per treatment for each row, except for columns n1 [a] and n2 [b].
n:The number of subjects in this reporting group affected by any occurrence of this adverse event, All Causalities.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v15.0) coding dictionary applied.

a. n1: The number of occurrences of treatment emergent all causalities AEs.
b. n2 (optional): The number of occurrences of treatment emergent causally related to treatment AEs.

Treatment-emergent SAEs by system organ class and preferred term (all causalities) are presented in Table 32.

Table 32: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Cyclosporine / Tacrolimus		Sirolimus Conc. Control	
Number of Subjects Evaluable for AEs	**210**		**389**	
Number (%) of Subjects With AEs	**77**	**(36.7)**	**193**	**(49.6)**
Number (%) of Subjects With AEs by:	**n**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Blood and lymphatic system disorders	5	(2.4)	15	(3.9)
Anaemia	3	(1.4)	11	(2.8)
Bone marrow failure	1	(0.5)	0	
Leukopenia	0		1	(0.3)
Lymphadenopathy	0		1	(0.3)
Lymphadenopathy mediastinal	0		1	(0.3)
Microcytic anaemia	0		1	(0.3)
Pancytopenia	1	(0.5)	1	(0.3)
Cardiac disorders	9	(4.3)	17	(4.4)
Acute myocardial infarction	0		1	(0.3)
Angina pectoris	1	(0.5)	2	(0.5)
Angina unstable	1	(0.5)	1	(0.3))
Atrial fibrillation	1	(0.5)	1	(0.3)
Atrial flutter	0		1	(0.3)
Atrioventricular block	0		1	(0.3)
Atrioventricular block complete	1	(0.5)	1	(0.3)
Cardiac disorder	0		1	(0.3)
Cardiac failure	1	(0.5)	4	(1)
Cardiomyopathy	1	(0.5)	0	
Congestive cardiomyopathy	0		1	(0.3)
Coronary artery disease	0		2	(0.5)
Coronary artery occlusion	1	(0.5)	0	
Left ventricular failure	0		1	(0.3)
Myocardial infarction	2	(1)	0	
Myocardial ischaemia	0		2	(0.5)
Pericardial effusion	0		1	(0.3)
Pericarditis	1	(0.5)	1	(0.3)
Sick sinus syndrome	0		1	(0.3)
Supraventricular tachycardia	1	(0.5)	0	
Tachycardia	1	(0.5)	0	
Congenital, familial and genetic disorders	1	(0.5)	0	
Haemophilia	1	(0.5)	0	
Endocrine disorders	1	(0.5)	0	
Goitre	1	(0.5)	0	
Eye disorders	1	(0.5)	3	(0.8)
Cataract	1	(0.5)	1	(0.3)
Diabetic retinopathy	0		1	(0.3)
Retinal detachment	0		1	(0.3)
Vitreous haemorrhage	0		1	(0.3)
Gastrointestinal disorders	17	(8.1)	48	(12.3)
Abdominal discomfort	1	(0.5)	1	(0.3)
Abdominal hernia	2	(1)	1	(0.3)
Abdominal pain	3	(1.4)	5	(1.3)
Abdominal pain upper	1	(0.5)	2	(0.5)
Abdominal tenderness	0		1	(0.3)
Acquired oesophageal web	0		1	(0.3)
Anal fistula	1	(0.5)	1	(0.3)
Anal stenosis	1	(0.5)	0	
Ascites	0		1	(0.3)
Colitis ulcerative	2	(1)	1	(0.3)
Constipation	0		1	(0.3)

Table 32: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Cyclosporine / Tacrolimus		Sirolimus Conc. Control	
Number of Subjects Evaluable for AEs	**210**		**389**	
Number (%) of Subjects With AEs	**77**	**(36.7)**	**193**	**(49.6)**
Number (%) of Subjects With AEs by:	**n**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Crohn's disease	1	(0.5)	0	
Diarrhoea	5	(2.4)	16	(4.1)
Faecalith	0		1	(0.3)
Faeces discoloured	1	(0.5)	0	
Food poisoning	0		1	(0.3)
Gastritis erosive	0		1	(0.3)
Gastrointestinal haemorrhage	2	(1)	3	(0.8)
Haematemesis	1	(0.5)	0	
Hernial eventration	1	(0.5)	0	
Ileus	1	(0.5)	1	(0.3)
Impaired gastric emptying	0		2	(0.5)
Inguinal hernia	0		2	(0.5)
Intestinal obstruction	0		1	(0.3)
Mesenteric vein thrombosis	0		1	(0.3)
Nausea	1	(0.5)	6	(1.5)
Oesophagitis	0		1	(0.3)
Pancreatitis	0		2	(0.5)
Rectal haemorrhage	1	(0.5)	0	
Sigmoiditis	0		1	(0.3)
Small intestinal obstruction	1	(0.5)	1	(0.3)
Stomatitis	0		1	(0.3)
Umbilical hernia	0		3	(0.8)
Umbilical hernia, obstructive	0		1	(0.3)
Upper gastrointestinal haemorrhage	0		1	(0.3)
Vomiting	2	(1)	10	(2.6)
General disorders and administration site conditions	13	(6.2)	33	(8.5)
Asthenia	2	(1)	2	(0.5)
Chest pain	4	(1.9)	4	(1)
Chills	3	(1.4)	2	(0.5)
Death	0		1	(0.3)
Device malfunction	1	(0.5)	0	
Device occlusion	0		1	(0.3)
Hernia	1	(0.5)	3	(0.8)
Hernia obstructive	0		1	(0.3)
Impaired healing	0		1	(0.3)
Medical device discomfort	1	(0.5)	0	
Multiorgan failure	0		1	(0.3)
Oedema peripheral	0		3	(0.8)
Pain	1	(0.5)	3	(0.8)
Pyrexia	8	(3.8)	16	(4.1)
Hepatobiliary disorders	4	(1.9)	14	(3.6)
Bile duct obstruction	0		1	(0.3)
Bile duct stenosis	1	(0.5)	6	(1.5)
Bile duct stone	0		2	(0.5)
Cholangitis	2	(1)	5	(1.3)
Cholangitis acute	0		1	(0.3)
Cholangitis sclerosing	0		1	(0.3)
Chronic hepatic failure	1	(0.5)	0	
Chronic hepatitis	0		1	(0.3)
Hepatic artery thrombosis	0		1	(0.3)
Hepatic failure	0		1	(0.3)

Table 32: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Cyclosporine / Tacrolimus		Sirolimus Conc. Control	
Number of Subjects Evaluable for AEs	**210**		**389**	
Number (%) of Subjects With AEs	**77**	**(36.7)**	**193**	**(49.6)**
Number (%) of Subjects With AEs by:	**n**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Hepatic steatosis	0		1	(0.3)
Hepatitis	1	(0.5)	0	
Hepatitis acute	1	(0.5)	0	
Jaundice	1	(0.5)	0	
Immune system disorders	1	(0.5)	2	(0.5)
Hypersensitivity	0		1	(0.3)
Transplant rejection	1	(0.5)	1	(0.3)
Infections and infestations	19	(9)	67	(17.2)
Abdominal wall abscess	0		2	(0.5)
Anal abscess	0		1	(0.3)
Appendicitis	1	(0.5)	1	(0.3)
Bacteraemia	1	(0.5)	1	(0.3)
Biliary sepsis	1	(0.5)	0	
Bronchitis	1	(0.5)	0	
Cellulitis	3	(1.4)	6	(1.5)
Cytomegalovirus infection	1	(0.5)	1	(0.3)
Device related infection	1	(0.5)	0	
Diarrhoea infectious	0		1	(0.3)
Diverticulitis	1	(0.5)	1	(0.3)
Enterobacter sepsis	0		1	(0.3)
Enterococcal infection	0		1	(0.3)
Erysipelas	0		2	(0.5)
Gastroenteritis	3	(1.4)	6	(1.5)
Gastroenteritis viral	2	(1	2	(0.5)
Haemophilus infection	0		1	(0.3)
Herpes oesophagitis	0		1	(0.3)
Herpes zoster	1	(0.5)	1	(0.3)
Infected skin ulcer	0		1	(0.3)
Influenza	0		1	(0.3)
Laryngitis	0		1	(0.3)
Liver abscess	0		1	(0.3)
Localised infection	0		1	(0.3)
Lower respiratory tract infection	0		2	(0.5)
Lymphangitis	0		1	(0.3)
Mycobacterium avium complex infection	0		1	(0.3)
Osteomyelitis	1	(0.5)	0	
Pneumonia	4	(1.9)	18	(4.6)
Postoperative wound infection	0		3	(0.8)
Pyelonephritis	0		1	(0.3)
Respiratory tract infection	0		2	(0.5)
Sepsis	2	(1)	6	(1.5)
Septic shock	0		1	(0.3)
Sinusitis	0		1	(0.3)
Subcutaneous abscess	0		1	(0.3)
Tooth abscess	0		1	(0.3)
Upper respiratory tract infection	1	(0.5)	5	(1.3)
Urinary tract infection	3	(1.4)	7	(1.8)
Urosepsis	1	(0.5)	0	
Viral upper respiratory tract infection	0		1	(0.3)
Wound infection staphylococcal	0		1	(0.3)

Table 32: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Cyclosporine / Tacrolimus		Sirolimus Conc. Control	
Number of Subjects Evaluable for AEs	**210**		**389**	
Number (%) of Subjects With AEs	**77**	**(36.7)**	**193**	**(49.6)**
Number (%) of Subjects With AEs by:	**n**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Injury, poisoning and procedural complications	7	(3.3)	30	(7.7)
Accidental overdose	0		3	(0.8)
Anastomotic stenosis	1	(0.5)	0	
Ankle fracture	1	(0.5)	0	
Biliary anastomosis complication	1	(0.5)	1	(0.3)
Chest injury	0		1	(0.3)
Drug administration error	0		1	(0.3)
Eye injury	0		1	(0.3)
Facial bones fracture	0		1	(0.3)
Hand fracture	0		1	(0.3)
Hip fracture	1	(0.5)	0	
In-stent coronary artery restenosis	0		1	(0.3)
Incision site pain	0		1	(0.3)
Incisional hernia	0		11	(2.8)
Joint dislocation	1	(0.5)	0	
Laceration	0		2	(0.5)
Overdose	0		2	(0.5)
Postoperative hernia	1	(0.5)	1	(0.3)
Procedural pain	1	(0.5)	1	(0.3)
Road traffic accident	0		1	(0.3)
Scapula fracture	1	(0.5)	0	
Seroma	0		1	(0.3)
Subdural haematoma	0		1	(0.3)
Toxicity to various agents	0		1	(0.3)
Wound decomposition	0		1	(0.3)
Wound necrosis	0		1	(0.3)
Investigations	12	(5.7)	33	(8.5)
Alanine aminotransferase increased	2	(1)	6	(1.5)
Aspartate aminotransferase increased	2	(1)	6	(1.5)
Blood alkaline phosphatase increased	0		6	(1.5)
Blood bilirubin increased	1	(0.5)	1	(0.3)
Blood creatinine increased	2	(1)	5	(1.3)
Blood potassium decreased	0		1	(0.3)
Blood pressure increased	0		1	(0.3)
Blood urea increased	0		2	(0.5)
Gamma-glutamyltransferase increased	0		3	(0.8)
Haematology test abnormal	1	(0.5)	0	
Hepatic enzyme increased	1	(0.5)	6	(1.5)
Hepatitis C virus test	0		1	(0.3)
International normalised ratio increased	0		1	(0.3)
Liver function test abnormal	2	(1)	9	(2.3)
Mammogram abnormal	1	(0.5)	0	
Urine colour abnormal	0		1	(0.3)
Weight decreased	1	(0.5)	1	(0.3)
Weight increased	1	(0.5)	0	
Metabolism and nutrition disorders	7	(3.3)	13	(3.3)
Acidosis	0		1	(0.3)
Dehydration	3	(1.4)	4	(1)
Diabetes mellitus	1	(0.5)	2	(0.5)
Diabetes mellitus inadequate control	1	(0.5v	0	
Diabetic ketoacidosis	0		1	(0.3)

Table 32: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Cyclosporine / Tacrolimus		Sirolimus Conc. Control	
Number of Subjects Evaluable for AEs	**210**		**389**	
Number (%) of Subjects With AEs	**77**	**(36.7)**	**193**	**(49.6)**
Number (%) of Subjects With AEs by:	**n**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Hyperglycaemia	1	(0.5)	2	(0.5)
Hyperkalaemia	1	(0.5)	0	
Hypertriglyceridaemia	0		1	(0.3)
Hypocalcaemia	0		1	(0.3)
Hypoglycaemia	0		2	(0.5)
Hypokalaemia	0		2	(0.5)
Hyponatraemia	1	(0.5))	0	
Musculoskeletal and connective tissue disorders	4	(1.9	14	(3.6)
Arthralgia	2	(1)	3	(0.8)
Arthritis	0		2	(0.5)
Back pain	0		3	(0.8)
Bursitis	0		1	(0.3)
Intervertebral disc protrusion	0		1	(0.3)
Muscle spasms	0		1	(0.3)
Neck pain	0		1	(0.3)
Osteoarthritis	2	(1)	2	(0.5)
Osteonecrosis	0		1	(0.3)
Pain in extremity	0		1	(0.3)
Spinal deformity	0		1	(0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28	(13.3)	28	(7.2)
Adenocarcinoma	0		1	(0.3)
Anal cancer	0		1	(0.3)
Basal cell carcinoma	8	(3.8)	9	(2.3)
Basosquamous carcinoma	2	(1)	0	
Bowen's disease	2	(1)	1	(0.3)
Colon adenoma	0		1	(0.3)
Colon cancer	2	(1)	2	(0.5)
Hepatic cancer metastatic	1	(0.5)	2	(0.5)
Hepatic neoplasm malignant	1	(0.5)	1	(0.3)
Lung cancer metastatic	1	(0.5)	0	
Lung neoplasm	0		1	(0.3)
Lymphoma	0		1	(0.3)
Malignant melanoma	2	(1)	1	(0.3)
Malignant melanoma in situ	1	(0.5)	0	
Malignant neoplasm of pleura	0		1	(0.3)
Metastases to lung	0		1	(0.3)
Metastasis	0		1	(0.3)
Metastatic malignant melanoma	0		1	(0.3)
Neoplasm	0		1	(0.3)
Neoplasm malignant	0		1	(0.3)
Neuroendocrine carcinoma of the skin	0		1	(0.3)
Non-small cell lung cancer	1	(0.5)	0	
Non-small cell lung cancer metastatic	1	(0.5)	0	
Pancreatic carcinoma metastatic	1	(0.5)	1	(0.3)
Prostate cancer	0		3	(0.8)
Prostate cancer metastatic	1	(0.5)	0	
Rectal cancer	1	(0.5)	0	
Signet-ring cell carcinoma	1	(0.5)	0	
Skin cancer	0		2	(0.5)
Squamous cell carcinoma	11	(5.2)	5	(1.3)
Squamous cell carcinoma of skin	3	(1.4)	3	(0.8)

Table 32: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Cyclosporine / Tacrolimus		Sirolimus Conc. Control	
Number of Subjects Evaluable for AEs	**210**		**389**	
Number (%) of Subjects With AEs	**77**	**(36.7)**	**193**	**(49.6)**
Number (%) of Subjects With AEs by:	**n**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Tongue neoplasm malignant stage unspecified	1	(0.5)	0	
Nervous system disorders	9	(4.3)	7	(1.8)
Aphasia	1	(0.5)	0	
Cerebrovascular accident	6	(2.9)	1	(0.3)
Convulsion	1	(0.5)	1	(0.3)
Dizziness	1	(0.5)	1	(0.3)
Dysarthria	1	(0.5)	0	
Headache	0		2	(0.5)
Hemiplegia	1	(0.5)	0	
Hypoaesthesia	0		1	(0.3)
Syncope	1	(0.5)	3	(0.8)
Transient ischaemic attack	1	(0.5)	0	
Pregnancy, puerperium and perinatal conditions	1	(0.5)	0	
Pregnancy	1	(0.5)	0	
Psychiatric disorders	1	(0.5)	2	(0.5)
Alcoholism	0		1	(0.3)
Depression	1	(0.5)	1	(0.3)
Renal and urinary disorders	5	(2.4)	26	(6.7)
Calculus urinary	0		1	(0.3)
Dysuria	1	(0.5)	1	(0.3)
Focal segmental glomerulosclerosis	0		1	(0.3)
Haematuria	1	(0.5)	0	
Hydronephrosis	1	(0.5)	0	
Nephritis allergic	0		1	(0.3)
Nephrolithiasis	1	(0.5)	3	(0.8)
Nephrosclerosis	0		1	(0.3)
Polyuria	0		1	(0.3)
Renal failure	1	(0.5)	9	(2.3)
Renal failure acute	2	(1)	9	(2.3)
Renal failure chronic	0		3	(0.8)
Renal impairment	1	(0.5)	4	(1)
Renal mass	0		1	(0.3)
Ureteric obstruction	1	(0.5)	0	
Urethral obstruction	1	(0.5)	0	
Urinary tract disorder	1	(0.5)	0	
Reproductive system and breast disorders	2	(1)	3	(0.8)
Adnexa uteri mass	1	(0.5)	0	
Benign prostatic hyperplasia	1	(0.5)	0	
Haematosalpinx	0		1	(0.3)
Ovarian cyst	0		3	(0.8)
Respiratory, thoracic and mediastinal disorders	4	(1.9)	22	(5.7)
Asthma	1	(0.5)	0	
Cough	1	(0.5)	4	(1)
Dyspnoea	0		9	(2.3)
Dyspnoea exertional	1	(0.5)	0	
Haemoptysis	1	(0.5)	0	
Haemothorax	0		1	(0.3)
Interstitial lung disease	0		1	(0.3)
Lung disorder	0		1	(0.3)
Lung infiltration	0		1	(0.3)
Oropharyngeal pain	0		1	(0.3)

Table 32: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Cyclosporine / Tacrolimus		Sirolimus Conc. Control	
Number of Subjects Evaluable for AEs	**210**		**389**	
Number (%) of Subjects With AEs	**77**	**(36.7)**	**193**	**(49.6)**
Number (%) of Subjects With AEs by:	**n**	**%**	**n**	**%**
System Organ Class				
Preferred Term				
Pharyngeal oedema	0		1	(0.3)
Pleural effusion	0		2	(0.5)
Pneumonitis	0		2	(0.5)
Pneumothorax	0		1	(0.3)
Productive cough	1	(0.5)	0	
Pulmonary embolism	1	(0.5)	0	
Pulmonary haemorrhage	0		1	(0.3)
Pulmonary hypertension	0		1	(0.3)
Pulmonary oedema	0		1	(0.3)
Vocal cord polyp	0		1	(0.3)
Skin and subcutaneous tissue disorders	3	(1.4)	8	(2.1)
Actinic keratosis	1	(0.5)	1	(0.3)
Erythema	0		1	(0.3)
Purpura	1	(0.5)	0	
Rash	0		1	(0.3)
Rash erythematous	1	(0.5)	0	
Rash generalised	0		2	(0.5)
Rash macular	0		1	(0.3)
Skin ulcer	0		1	(0.3)
Swelling face	0		1	(0.3)
Surgical and medical procedures	0		3	(0.8)
Incisional hernia repair	0		1	(0.3)
Surgery	0		1	(0.3)
Umbilical hernia repair	0		1	(0.3)
Vascular disorders	3	(1.4)	9	(2.3)
Aortic stenosis	0		1	(0.3)
Arterial thrombosis	0		1	(0.3)
Deep vein thrombosis	1	(0.5)	0	
Haematoma	1	(0.5)	3	(0.8)
Hypertension	1	(0.5)	1	(0.3)
Hypotension	0		1	(0.3)
Orthostatic hypotension	0		1	(0.3)
Peripheral ischaemia	0		1	(0.3)
Steal syndrome	1	(0.5)	0	
Subclavian artery stenosis	0		1	(0.3)

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (v15.0) coding dictionary applied.

Treatment-emergent SAEs by system organ class and preferred term are presented in Table 33.

Table 33: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Cyclosporine / Tacrolimus				Sirolimus Concentration Control			
Number (%) of Subjects Evaluable for AEs	**210**				**389**			
Number (%) of Subjects With AEs	**77**	**(36.7)**			**193**	**(49.6)**		
Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Blood and lymphatic system disorders	5	(2.4)	8	2	15	(3.9)	23	19
Anaemia	3	(1.4)	6	1	11	(2.8)	15	12
Bone marrow failure	1	(0.5)	1	0	0		0	0
Leukopenia	0		0	0	1	(0.3)	1	1
Lymphadenopathy	0		0	0	1	(0.3)	1	1
Lymphadenopathy mediastinal	0		0	0	1	(0.3)	1	0
Microcytic anaemia	0		0	0	1	(0.3)	4	4
Pancytopenia	1	(0.5)	1	1	1	(0.3)	1	1
Cardiac disorders	9	(4.3)	16	0	17	(4.4)	25	7
Acute myocardial infarction	0		0	0	1	(0.3)	1	1
Angina pectoris	1	(0.5)	1	0	2	(0.5)	2	1
Angina unstable	1	(0.5)	1	0	1	(0.3)	2	2
Atrial fibrillation	1	(0.5)	5	0	1	(0.3)	1	0
Atrial flutter	0		0	0	1	(0.3)	1	0
Atrioventricular block	0		0	0	1	(0.3)	1	0
Atrioventricular block complete	1	(0.5)	1	0	1	(0.3)	1	0
Cardiac disorder	0		0	0	1	(0.3)	1	0
Cardiac failure	1	(0.5)	1	0	4	(1.0)	4	1
Cardiomyopathy	1	(0.5)	1	0	0		0	0
Congestive cardiomyopathy	0		0	0	1	(0.3)	1	0
Coronary artery disease	0		0	0	2	(0.5)	3	0
Coronary artery occlusion	1	(0.5)	1	0	0		0	0
Left ventricular failure	0		0	0	1	(0.3)	1	0
Myocardial infarction	2	(1.0)	2	0	0		0	0
Myocardial ischaemia	0		0	0	2	(0.5)	2	0
Pericardial effusion	0		0	0	1	(0.3)	2	2
Pericarditis	1	(0.5)	1	0	1	(0.3)	1	0
Sick sinus syndrome	0		0	0	1	(0.3)	1	0
Supraventricular tachycardia	1	(0.5)	1	0	0		0	0
Tachycardia	1	(0.5)	1	0	0		0	0
Congenital, familial and genetic disorders	1	(0.5)	1	0	0		0	0
Haemophilia	1	(0.5)	1	0	0		0	0
Endocrine disorders	1	(0.5)	1	0	0		0	0
Goitre	1	(0.5)	1	0	0		0	0
Eye disorders	1	(0.5)	1	0	3	(0.8)	4	0
Cataract	1	(0.5)	1	0	1	(0.3)	1	0
Diabetic retinopathy	0		0	0	1	(0.3)	1	0
Retinal detachment	0		0	0	1	(0.3)	1	0
Vitreous haemorrhage	0		0	0	1	(0.3)	1	0
Gastrointestinal disorders	17	(8.1)	32	0	48	(12.3)	84	22
Abdominal discomfort	1	(0.5)	1	0	1	(0.3)	1	0
Abdominal hernia	2	(1.0)	2	0	1	(0.3)	1	0
Abdominal pain	3	(1.4)	4	0	5	(1.3)	8	3
Abdominal pain upper	1	(0.5)	1	0	2	(0.5)	2	0
Abdominal tenderness	0		0	0	1	(0.3)	1	1
Acquired oesophageal web	0		0	0	1	(0.3)	1	0
Anal fistula	1	(0.5)	1	0	1	(0.3)	1	0
Anal stenosis	1	(0.5)	1	0	0		0	0
Ascites	0		0	0	1	(0.3)	1	0
Colitis ulcerative	2	(1.0)	3	0	1	(0.3)	1	1
Constipation	0		0	0	1	(0.3)	1	0

Table 33: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Cyclosporine / Tacrolimus				Sirolimus Concentration Control			
Number (%) of Subjects Evaluable for AEs	**210**				**389**			
Number (%) of Subjects With AEs	**77**	**(36.7)**			**193**	**(49.6)**		
Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Crohn's disease	1	(0.5)	1	0	0		0	0
Diarrhoea	5	(2.4)	5	0	16	(4.1)	22	8
Faecalith	0		0	0	1	(0.3)	1	0
Faeces discoloured	1	(0.5)	1	0	0		0	0
Food poisoning	0		0	0	1	(0.3)	1	0
Gastritis erosive	0		0	0	1	(0.3)	1	1
Gastrointestinal haemorrhage	2	(1.0)	2	0	3	(0.8)	3	0
Haematemesis	1	(0.5)	1	0	0		0	0
Hernial eventration	1	(0.5)	2	0	0		0	0
Ileus	1	(0.5)	1	0	1	(0.3)	1	0
Impaired gastric emptying	0		0	0	2	(0.5)	3	0
Inguinal hernia	0		0	0	2	(0.5)	3	0
Intestinal obstruction	0		0	0	1	(0.3)	1	0
Mesenteric vein thrombosis	0		0	0	1	(0.3)	2	2
Nausea	1	(0.5)	1	0	6	(1.5)	6	1
Oesophagitis	0		0	0	1	(0.3)	1	1
Pancreatitis	0		0	0	2	(0.5)	2	0
Rectal haemorrhage	1	(0.5)	2	0	0		0	0
Sigmoiditis	0		0	0	1	(0.3)	1	0
Small intestinal obstruction	1	(0.5)	1	0	1	(0.3)	1	0
Stomatitis	0		0	0	1	(0.3)	2	2
Umbilical hernia	0		0	0	3	(0.8)	3	0
Umbilical hernia, obstructive	0		0	0	1	(0.3)	1	0
Upper gastrointestinal haemorrhage	0		0	0	1	(0.3)	1	0
Vomiting	2	(1.0)	2	0	10	(2.6)	10	2
General disorders and administration site conditions	13	(6.2)	21	1	33	(8.5)	55	20
Asthenia	2	(1.0)	2	0	2	(0.5)	3	0
Chest pain	4	(1.9)	4	0	4	(1.0)	5	2
Chills	3	(1.4)	3	0	2	(0.5)	2	2
Death	0		0	0	1	(0.3)	1	0
Device malfunction	1	(0.5)	1	0	0		0	0
Device occlusion	0		0	0	1	(0.3)	1	0
Hernia	1	(0.5)	1	0	3	(0.8)	5	0
Hernia obstructive	0		0	0	1	(0.3)	1	0
Impaired healing	0		0	0	1	(0.3)	2	0
Medical device discomfort	1	(0.5)	1	0	0		0	0
Multi-organ failure	0		0	0	1	(0.3)	1	0
Oedema peripheral	0		0	0	3	(0.8)	5	5
Pain	1	(0.5)	1	0	3	(0.8)	3	1
Pyrexia	8	(3.8)	8	1	16	(4.1)	26	10
Hepatobiliary Disorders	4	(1.9)	8	2	14	(3.6)	29	4
Bile duct obstruction	0		0	0	1	(0.3)	1	0
Bile duct stenosis	1	(0.5)	2	0	6	(1.5)	9	0
Bile duct stone	0		0	0	2	(0.5)	3	0
Cholangitis	2	(1.0)	2	0	5	(1.3)	9	2
Cholangitis acute	0		0	0	1	(0.3)	1	0
Cholangitis sclerosing	0		0	0	1	(0.3)	1	0
Chronic hepatic failure	1	(0.5)	1	0	0		0	0
Chronic hepatitis	0		0	0	1	(0.3)	1	1
Hepatic artery thrombosis	0		0	0	1	(0.3)	2	0
Hepatic failure	0		0	0	1	(0.3)	1	0

Table 33: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Cyclosporine / Tacrolimus				Sirolimus Concentration Control			
Number (%) of Subjects Evaluable for AEs	**210**				**389**			
Number (%) of Subjects With AEs	**77**	**(36.7)**			**193**	**(49.6)**		
Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Hepatic steatosis	0		0	0	1	(0.3)	1	1
Hepatitis	1	(0.5)	1	1	0		0	0
Hepatitis acute	1	(0.5)	1	1	0		0	0
Jaundice	1	(0.5)	1	0	0		0	0
Immune system disorders	1	(0.5)	2	2	2	(0.5)	3	3
Hypersensitivity	0		0	0	1	(0.3)	2	2
Transplant **rejection**	1	(0.5)	2	2	1	(0.3)	1	1
Infections and infestations	19	(9.0)	35	5	67	(17.2)	110	47
Abdominal wall abscess	0		0	0	2	(0.5)	2	0
Anal abscess	0		0	0	1	(0.3)	9	9
Appendicitis	1	(0.5)	1	0	1	(0.3)	1	0
Bacteraemia	1	(0.5)	1	0	1	(0.3)	1	1
Biliary sepsis	1	(0.5)	3	0	0		0	0
Bronchitis	1	(0.5)	1	0	0		0	0
Cellulitis	3	(1.4)	3	1	6	(1.5)	7	0
Cytomegalovirus infection	1	(0.5)	1	0	1	(0.3)	1	0
Device related infection	1	(0.5)	1	0	0		0	0
Diarrhoea infectious	0		0	0	1	(0.3)	1	0
Diverticulitis	1	(0.5)	1	0	1	(0.3)	2	0
Enterobacter sepsis	0		0	0	1	(0.3)	2	2
Enterococcal infection	0		0	0	1	(0.3)	1	0
Erysipelas	0		0	0	2	(0.5)	3	2
Gastroenteritis	3	(1.4)	3	0	6	(1.5)	7	2
Gastroenteritis viral	2	(1.0)	2	0	2	(0.5)	2	0
Haemophilus infection	0		0	0	1	(0.3)	1	1
Herpes oesophagitis	0		0	0	1	(0.3)	2	2
Herpes zoster	1	(0.5)	2	2	1	(0.3)	1	1
Infected skin ulcer	0		0	0	1	(0.3)	1	0
Influenza	0		0	0	1	(0.3)	1	0
Laryngitis	0		0	0	1	(0.3)	1	0
Liver abscess	0		0	0	1	(0.3)	1	0
Localised infection	0		0	0	1	(0.3)	2	2
Lower respiratory tract infection	0		0	0	2	(0.5)	3	0
Lymphangitis	0		0	0	1	(0.3)	2	0
Mycobacterium avium complex infection	0		0	0	1	(0.3)	1	1
Osteomyelitis	1	(0.5)	1	0	0		0	0
Pneumonia	4	(1.9)	5	2	18	(4.6)	19	12
Postoperative wound infection	0		0	0	3	(0.8)	4	2
Pyelonephritis	0		0	0	1	(0.3)	1	0
Respiratory tract infection	0		0	0	2	(0.5)	3	2
Sepsis	2	(1.0)	3	0	6	(1.5)	7	4
Septic shock	0		0	0	1	(0.3)	1	1
Sinusitis	0		0	0	1	(0.3)	1	1
Subcutaneous abscess	0		0	0	1	(0.3)	1	0
Tooth abscess	0		0	0	1	(0.3)	1	0
Upper respiratory tract infection	1	(0.5)	1	0	5	(1.3)	5	1
Urinary tract infection	3	(1.4)	3	0	7	(1.8)	10	0
Urosepsis	1	(0.5)	3	0	0		0	0
Viral upper respiratory tract infection	0		0	0	1	(0.3)	1	1
Wound infection staphylococcal	0		0	0	1	(0.3)	1	0
Injury, poisoning and procedural complications	7	(3.3)	9	0	30	(7.7)	41	13

Table 33: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Cyclosporine / Tacrolimus				Sirolimus Concentration Control			
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Number (%) of Subjects With AEs	**77**	**(36.7)**			**193**	**(49.6)**		
Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Accidental overdose	0		0	0	3	(0.8)	3	0
Anastomotic stenosis	1	(0.5)	2	0	0		0	0
Ankle fracture	1	(0.5)	1	0	0		0	0
Biliary anastomosis complication	1	(0.5)	1	0	1	(0.3)	1	0
Chest injury	0		0	0	1	(0.3)	1	0
Drug administration error	0		0	0	1	(0.3)	2	2
Eye injury	0		0	0	1	(0.3)	1	0
Facial bones fracture	0		0	0	1	(0.3)	1	0
Hand fracture	0		0	0	1	(0.3)	1	0
Hip fracture	1	(0.5)	1	0	0		0	0
In-stent coronary artery restenosis	0		0	0	1	(0.3)	1	0
Incision site pain	0		0	0	1	(0.3)	1	0
Incisional hernia	0		0	0	11	(2.8)	13	1
Joint dislocation	1	(0.5)	1	0	0		0	0
Laceration	0		0	0	2	(0.5)	2	0
Overdose	0		0	0	2	(0.5)	3	3
Postoperative hernia	1	(0.5)	1	0	1	(0.3)	2	2
Procedural pain	1	(0.5)	1	0	1	(0.3)	1	0
Road traffic accident	0		0	0	1	(0.3)	1	0
Scapula fracture	1	(0.5)	1	0	0		0	0
Seroma	0		0	0	1	(0.3)	2	2
Subdural haematoma	0		0	0	1	(0.3)	1	0
Toxicity to various agents	0		0	0	1	(0.3)	2	2
Wound decomposition	0		0	0	1	(0.3)	1	0
Wound necrosis	0		0	0	1	(0.3)	1	1
Investigations	12	(5.7)	29	11	33	(8.5)	67	39
Alanine aminotransferase increased	2	(1.0)	4	3	6	(1.5)	9	7
Aspartate aminotransferase increased	2	(1.0)	4	3	6	(1.5)	9	7
Blood alkaline phosphatase increased	0		0	0	6	(1.5)	8	4
Blood bilirubin increased	1	(0.5)	2	2	1	(0.3)	1	0
Blood creatinine increased	2	(1.0)	3	3	5	(1.3)	5	1
Blood potassium decreased	0		0	0	1	(0.3)	1	1
Blood pressure increased	0		0	0	1	(0.3)	1	0
Blood urea increased	0		0	0	2	(0.5)	2	1
Gamma-glutamyltransferase increased	0		0	0	3	(0.8)	6	4
Haematology test abnormal	1	(0.5)	5	0	0		0	0
Hepatic enzyme increased	1	(0.5)	3	0	6	(1.5)	8	7
Hepatitis C virus test	0		0	0	1	(0.3)	2	0
International normalised ratio increased	0		0	0	1	(0.3)	1	0
Liver function test abnormal	2	(1.0)	4	0	9	(2.3)	12	6
Mammogram abnormal	1	(0.5)	2	0	0		0	0
Urine colour abnormal	0		0	0	1	(0.3)	1	0
Weight decreased	1	(0.5)	1	0	1	(0.3)	1	1
Weight increased	1	(0.5)	1	0	0		0	0
Metabolism and nutrition disorders	7	(3.3)	11	3	13	(3.3)	20	6
Acidosis	0		0	0	1	(0.3)	1	0
Dehydration	3	(1.4)	3	0	4	(1.0)	7	1
Diabetes mellitus	1	(0.5)	2	1	2	(0.5)	2	1
Diabetes mellitus inadequate control	1	(0.5)	1	1	0		0	0
Diabetic ketoacidosis	0		0	0	1	(0.3)	1	0
Hyperglycaemia	1	(0.5)	3	0	2	(0.5)	2	1

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Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Hyperkalaemia	1	(0.5)	1	1	0		0	0
Hypertriglyceridaemia	0		0	0	1	(0.3)	1	1
Hypocalcaemia	0		0	0	1	(0.3)	1	0
Hypoglycaemia	0		0	0	2	(0.5)	2	0
Hypokalaemia	0		0	0	2	(0.5)	2	1
Hyponatraemia	1	(0.5)	1	0	0		0	0
Metabolic disorder	0		0	0	1	(0.3)	1	1
Musculoskeletal and connective tissue disorders	4	(1.9)	5	0	14	(3.6)	19	5
Arthralgia	2	(1.0)	2	0	3	(0.8)	3	1
Arthritis	0		0	0	2	(0.5)	4	2
Back pain	0		0	0	3	(0.8)	3	0
Bursitis	0		0	0	1	(0.3)	1	0
Intervertebral disc protrusion	0		0	0	1	(0.3)	1	0
Muscle spasms	0		0	0	1	(0.3)	1	0
Neck pain	0		0	0	1	(0.3)	1	0
Osteoarthritis	2	(1.0)	3	0	2	(0.5)	2	1
Osteonecrosis	0		0	0	1	(0.3)	1	1
Pain in extremity	0		0	0	1	(0.3)	1	0
Spinal deformity	0		0	0	1	(0.3)	1	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	28	(13.3)	58	35	28	(7.2)	63	24
Adenocarcinoma	0		0	0	1	(0.3)	2	0
Anal cancer	0		0	0	1	(0.3)	1	1
Basal cell carcinoma	8	(3.8)	13	10	9	(2.3)	18	6
Basosquamous carcinoma	2	(1.0)	2	2	0		0	0
Bowen's disease	2	(1.0)	4	4	1	(0.3)	1	1
Colon adenoma	0		0	0	1	(0.3)	1	1
Colon cancer	2	(1.0)	2	0	2	(0.5)	3	0
Hepatic cancer metastatic	1	(0.5)	1	0	2	(0.5)	2	1
Hepatic neoplasm malignant	1	(0.5)	2	0	1	(0.3)	1	0
Lung cancer metastatic	1	(0.5)	1	0	0		0	0
Lung neoplasm	0		0	0	1	(0.3)	1	0
Lymphoma	0		0	0	1	(0.3)	1	0
Malignant melanoma	2	(1.0)	3	3	1	(0.3)	2	0
Malignant melanoma in situ	1	(0.5)	1	1	0		0	0
Malignant neoplasm of pleura	0		0	0	1	(0.3)	1	0
Metastases to lung	0		0	0	1	(0.3)	1	0
Metastasis	0		0	0	1	(0.3)	1	1
Metastatic malignant melanoma	0		0	0	1	(0.3)	3	3
Neoplasm	0		0	0	1	(0.3)	1	1
Neoplasm malignant	0		0	0	1	(0.3)	1	1
Neuroendocrine carcinoma of the skin	0		0	0	1	(0.3)	1	0
Non-small cell lung cancer	1	(0.5)	1	0	0		0	0
Non-small cell lung cancer metastatic	1	(0.5)	1	0	0		0	0
Pancreatic carcinoma metastatic	1	(0.5)	2	0	1	(0.3)	1	0
Prostate cancer	0		0	0	3	(0.8)	4	1
Prostate cancer metastatic	1	(0.5)	2	2	0		0	0
Rectal cancer	1	(0.5)	1	0	0		0	0
Signet-ring cell carcinoma	1	(0.5)	1	0	0		0	0
Skin cancer	0		0	0	2	(0.5)	2	1
Squamous cell carcinoma	11	(5.2)	16	11	5	(1.3)	9	4

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Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Squamous cell carcinoma of skin	3	(1.4)	3	2	3	(0.8)	5	2
Tongue neoplasm malignant stage unspecified	1	(0.5)	2	0	0		0	0
Nervous system disorders	9	(4.3)	16	6	7	(1.8)	10	3
Aphasia	1	(0.5)	1	0	0		0	0
Cerebrovascular accident	6	(2.9)	8	4	1	(0.3)	1	0
Convulsion	1	(0.5)	1	0	1	(0.3)	1	0
Dizziness	1	(0.5)	1	0	1	(0.3)	2	2
Dysarthria	1	(0.5)	2	2	0		0	0
Headache	0		0	0	2	(0.5)	2	0
Hemiplegia	1	(0.5)	1	0	0		0	0
Hypoaesthesia	0		0	0	1	(0.3)	1	0
Syncope	1	(0.5)	1	0	3	(0.8)	3	1
Transient ischaemic attack	1	(0.5)	1	0	0		0	0
Pregnancy, puerperium and perinatal conditions	1	(0.5)	1	0	0		0	0
Pregnancy	1	(0.5)	1	0	0		0	0
Psychiatric disorders	1	(0.5)	1	0	2	(0.5)	2	0
Alcoholism	0		0	0	1	(0.3)	1	0
Depression	1	(0.5)	1	0	1	(0.3)	1	0
Renal and urinary disorders	5	(2.4)	13	4	26	(6.7)	38	15
Calculus urinary	0		0	0	1	(0.3)	1	0
Dysuria	1	(0.5)	1	0	1	(0.3)	1	0
Focal segmental glomerulosclerosis	0		0	0	1	(0.3)	1	0
Haematuria	1	(0.5)	1	0	0		0	0
Hydronephrosis	1	(0.5)	1	0	0		0	0
Nephritis allergic	0		0	0	1	(0.3)	1	0
Nephrolithiasis	1	(0.5)	1	0	3	(0.8)	3	0
Nephrosclerosis	0		0	0	1	(0.3)	1	1
Polyuria	0		0	0	1	(0.3)	1	0
Renal failure	1	(0.5)	1	1	9	(2.3)	10	5
Renal failure acute	2	(1.0)	3	2	9	(2.3)	10	3
Renal failure chronic	0		0	0	3	(0.8)	3	2
Renal impairment	1	(0.5)	1	1	4	(1.0)	5	4
Renal mass	0		0	0	1	(0.3)	1	0
Ureteric obstruction	1	(0.5)	1	0	0		0	0
Urethral obstruction	1	(0.5)	2	0	0		0	0
Urinary tract disorder	1	(0.5)	1	0	0		0	0
Reproductive system and breast disorders	2	(1.0)	3	0	3	(0.8)	4	0
Adnexa uteri mass	1	(0.5)	1	0	0		0	0
Benign prostatic hyperplasia	1	(0.5)	2	0	0		0	0
Haematosalpinx	0		0	0	1	(0.3)	1	0
Ovarian cyst	0		0	0	3	(0.8)	3	0
Respiratory, thoracic and mediastinal disorders	4	(1.9)	7	0	22	(5.7)	34	18
Asthma	1	(0.5)	1	0	0		0	0
Cough	1	(0.5)	1	0	4	(1.0)	5	4
Dyspnoea	0		0	0	9	(2.3)	9	4
Dyspnoea exertional	1	(0.5)	1	0	0		0	0
Haemoptysis	1	(0.5)	2	0	0		0	0
Haemothorax	0		0	0	1	(0.3)	3	0
Interstitial lung disease	0		0	0	1	(0.3)	3	3
Lung disorder	0		0	0	1	(0.3)	1	1
Lung infiltration	0		0	0	1	(0.3)	1	1

Table 33: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Cyclosporine / Tacrolimus				Sirolimus Concentration Control			
Number (%) of Subjects Evaluable for AEs	**210**				**389**			
Number (%) of Subjects With AEs	**77**	**(36.7)**			**193**	**(49.6)**		
Number (%) of Subjects with AEs by:	**n**	**%**	**n1[a]**	**n2[b]**	**n**	**%**	**n1[a]**	**n2[b]**
System Organ Class								
Preferred Term								
Oropharyngeal pain	0		0	0	1	(0.3)	1	1
Pharyngeal oedema	0		0	0	1	(0.3)	1	0
Pleural effusion	0		0	0	2	(0.5)	2	0
Pneumonitis	0		0	0	2	(0.5)	2	2
Pneumothorax	0		0	0	1	(0.3)	1	0
Productive cough	1	(0.5)	1	0	0		0	0
Pulmonary embolism	1	(0.5)	1	0	0		0	0
Pulmonary haemorrhage	0		0	0	1	(0.3)	1	0
Pulmonary hypertension	0		0	0	1	(0.3)	1	0
Pulmonary oedema	0		0	0	1	(0.3)	2	2
Vocal cord polyp	0		0	0	1	(0.3)	1	0
Skin and subcutaneous tissue disorders	3	(1.4)	3	2	8	(2.1)	17	13
Actinic keratosis	1	(0.5)	1	1	1	(0.3)	1	1
Erythema	0		0	0	1	(0.3)	1	0
Purpura	1	(0.5)	1	0	0		0	0
Rash	0		0	0	1	(0.3)	3	3
Rash erythematous	1	(0.5)	1	1	0		0	0
Rash generalised	0		0	0	2	(0.5)	4	4
Rash macular	0		0	0	1	(0.3)	3	3
Skin ulcer	0		0	0	1	(0.3)	3	0
Swelling face	0		0	0	1	(0.3)	2	2
Surgical and medical procedures	0	0	0	0	3	(0.8)	3	0
Incisional hernia repair	0		0	0	1	(0.3)	1	0
Surgery	0		0	0	1	(0.3)	1	0
Umbilical hernia repair	0		0	0	1	(0.3)	1	0
Vascular disorders	3	(1.4)	8	0	9	(2.3)	12	4
Aortic stenosis	0		0	0	1	(0.3)	2	2
Arterial thrombosis	0		0	0	1	(0.3)	1	1
Deep vein thrombosis	1	(0.5)	3	0	0		0	0
Haematoma	1	(0.5)	2	0	3	(0.8)	4	0
Hypertension	1	(0.5)	1	0	1	(0.3)	1	0
Hypotension	0		0	0	1	(0.3)	1	1
Orthostatic hypotension	0		0	0	1	(0.3)	1	0
Peripheral ischaemia	0		0	0	1	(0.3)	1	0
Steal syndrome	1	(0.5)	2	0	0		0	0
Subclavian artery stenosis	0		0	0	1	(0.3)	1	0

Except for 'n1' and 'n2' Subjects are only counted once per treatment for each row.
n = The number of subjects in this reporting group affected by any occurrence of this adverse event, All Causalities.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v15.0) coding dictionary applied.
a. n1: The number of Occurrences of Treatment Emergent All Causalities AEs.
b. n2: The number of Occurrences of Treatment Emergent Causally Related to Treatment AEs.

Death summary is presented in Table 34.

Table 34: Death Summary

	Pre-Randomization (N=767)	
Number of Subjects Evaluable for AEs	**599**	
Number of Subjects with AEs Leading to Death, by:	**n**	**n1[a]**
System Organ Class **Preferred Term**		
Cardiac disorders	2	1
Acute myocardial infarction	1	1
Cardio-respiratory arrest	1	0
Gastrointestinal disorders	1	0
Gastrointestinal haemorrhage	1	0
General disorders and administration site conditions	2	0
Accidental death	1	0
Sudden death	1	0
Hepatobiliary disorders	3	0
Acute hepatic failure	1	0
Bile duct stenosis	1	0
Hepatic failure	1	0
Infections and infestations	4	4
Abscess	1	1
Pneumonia	1	1
Pseudomonal sepsis	1	1
Septic shock	1	1
Metabolism and nutrition disorders	1	0
Type 2 diabetes mellitus	1	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	14	6
Adenocarcinoma	1	0
Burkitt's lymphoma	1	0
Gallbladder cancer recurrent	1	0
Laryngeal cancer	1	0
Lung adenocarcinoma metastatic	2	2
Malignant melanoma	2	2
Mediastinum neoplasm	1	1
Metastasis	1	1
Neoplasm malignant	1	0
Pancreatic carcinoma metastatic	2	1
Skin cancer metastatic	1	0
Nervous system disorders	2	2
Cerebrovascular accident	1	1
Embolic stroke	1	1
Respiratory, thoracic and mediastinal disorders	2	0
Haemoptysis	1	0
Pulmonary embolism	1	0
Total number of fatalities from AEs[b]	30	
Total number of deaths all causes[c]	30	

A subject death can be associated with more than one treatment if the first onset date of the case falls within multiple treatment group periods
MedDRA v.17.0 coding dictionary applied.
AE = adverse event; SAE = serious adverse event.

a. n1: The number of AEs associated with a fatality, and thought to be associated or related to treatment. A fatality can be associated with multiple events
b. Total number of deaths in this reporting group thought to be causally related to adverse events.
c. Total number of deaths (all causes) in this reporting group. This includes deaths not related to the trial.

CONCLUSIONS:

This study was the first large-scale, prospective, randomized, parallel-group clinical trial of conversion from CNI-based maintenance immunosuppression to SRL-based maintenance immunosuppression in liver allograft recipients. The purpose of the study was to evaluate the safety, tolerability, and efficacy of a SRL conversion regimen versus continuation of CNI-based immunosuppression in stable liver transplant recipients, 6 to 144 months after transplantation. A total of 607 subjects were randomly assigned to the study, 599 subjects received at least 1 dose of study drug, and were thus included in the safety analysis; all 607 subjects were included in the efficacy analysis.

ITT analysis of the primary efficacy endpoint (ie, Baseline-adjusted Cockroft-Gault GFR at 1 year) demonstrated -4.5 mL/min and -3.1 mL/min adjusted mean changes from Baseline GFR for the SRLconversion and CNI continuation treatment cohorts, respectively; the resulting treatment difference was not statistically significant (p=0.342). Failure of the study to meet its primary efficacy endpoint may be, at least partly, due to the broad spectrum of preexisting chronic renal injury present in a subset of randomly assigned subjects who had been exposed to CNI-based immunosuppression for up to 12 years following liver transplantation.

In another study (A Randomized, Open-Label, Comparative Evaluation of Conversion From Calcineurin Inhibitors to Sirolimus Versus Continued Use of Calcineurin Inhibitors in Renal Allograft Recipients [NCT00038948]), post hoc, exploratory, multivariate analyses identified baseline GFR as an independent, statistically significant predictor of the degree of improvement in renal function observed at 12 and 24 months after SRLconversion. Preexisting glomerular disease and the degree of abnormal urinary protein excretion were additional independent predictors of the extent to which subjects were likely to benefit from conversion from CNI- to SRL-based immunosuppression at 6 to 120 months after transplantation. In the absence of data on urinary protein excretion and the type and severity of native renal histopathology at Baseline, the extent of preexisting renal parenchymal injury cannot be established more definitively in the current liver conversion study. However, subjects were eligible for enrollment with calculated GFRs as low as 40 mL/min, a level consistent with a moderate degree of chronic renal insufficiency. Thus, the renal parenchymal injury present in a number of subjects at Baseline may have prevented them from realizing the same degree of improvement in renal function following SRL conversion as those subjects who received transplants more recently, and had healthier kidneys at the time of randomization (shorter period of cumulative exposure to CNIs).

In addition to the presence of varying degrees of renal injury, the significantly higher rate of premature withdrawal from assigned treatment observed in the SRLconversion cohort also likely contributed to the failure to achieve the primary efficacy endpoint. Most of these subjects were discontinued from SRLand converted back to CNI-based immunosuppression, so that their observed change from Baseline GFR did not reflect the impact of having been discontinued from CNI for a full year.

The safety results were as follows:

- The rates of the primary safety endpoint, the composite of subject and graft survival at 1 year, were 93.4% and 94.4% for the sirolimus conversion and CNI continuation cohorts, respectively, a difference that was not statistically significant in the ITT analysis (p=0.56).

- Conversion to sirolimus was associated with a numerically lower rate of subject survival when compared to that for CNI continuation, which was not statistically significant (96.7% vs 98.6%, respectively, p=0.192).

- At 1 year, the rates of biopsy-confirmed acute rejection were 11.7% and 6.1% in the sirolimus conversion and CNI continuation cohorts, respectively, a difference that was statistically significant (p=0.017).

- During the first year of follow-up, discontinuations from assigned therapy occurred for 36.0% and 11.0% of sirolimus conversion and CNI continuation subjects, respectively, a statistically significant difference (p<0.001). AEs were the most common reason for premature discontinuation (23.9% and 5.2% for sirolimus conversion subjects and CNI continuation subjects, respectively, p<0.001).

- Overall, significantly more sirolimus conversion than CNI continuation subjects were reported to have experienced at least 1 TEAE (excluding infections and malignancies) through month 12 of the study, (99.0% vs 84.8%, respectively, p<0.001). The incidence of infection-related TEAEs through month 12 of the study was also significantly higher in the sirolimus conversion cohort versus the CNI continuation cohort (59.6% versus 44.8%, respectively, p<0.001), which was primarily attributable to differences in the incidence of pneumonia (3.1% vs 0.5%, respectively) and herpes simplex (7.5% vs 0.5%, respectively). The incidence of malignancies through month 12 of the study was numerically lower in the sirolimus conversion cohort as compared to CNI continuation: 3.3% and 6.2%, respectively.

- Investigator-reported TEAEs that were significantly more frequent following sirolimus conversion were consistent with the known safety profile of sirolimus. Of note, among the 607 subjects randomly assigned to the study, only a single case of hepatic artery thrombosis was reported, in a subject randomly assigned to sirolimus conversion.

The significantly higher rate of acute allograft rejection in the sirolimus conversion cohort was primarily attributable to: (a) the abrupt change in immunosuppression, because most of these events occurred within the first 3 months thereafter; and (b) the fact that, for at least some of these subjects, sirolimus trough levels had been below the protocol-specified target range before clinical onset of the event. Concentration effect relationship analysis failed to detect differences in sirolimus $C_{min,TN}$ between those experiencing rejection and those who did not.

The numerically lower rate of subject survival for sirolimus versus CNI treatment demonstrated in this study was partly attributable to the randomization—in violation of the protocol—of several subjects who, in retrospect, had clinical documentation of preexisting

malignancy at the time of their enrollment, and several others in whom a malignancy was strongly suspected on the basis of disease recurrence that was diagnosed shortly after randomization. All but one of these subjects had been allocated to the sirolimus conversion cohort.

No new or unexpected safety findings were identified in this clinical trial. The events reported were all expected on the basis of the known adverse event profile of sirolimus, as documented in current product labeling.

The overall rates for the primary endpoint of graft loss were 6.6% and 5.6% for the SRL conversion and CNI continuation cohorts, respectively. The 95% CI for the weighted difference in rates of graft loss [-5.2, 1.8] did not meet the criterion for declaring noninferiority that was pre-specified as the lower bound of the 95% CI for the difference in rates of graft loss not being less than 5%. The study therefore failed to meet its primary safety endpoint.

There was no significant difference between the 2 treatment groups in the rates of graft survival (graft loss being defined as death or retransplantation) which were 94.9% and 96.3% for the SRL conversion and CNI continuation cohorts, respectively (p=0.442). The large majority of graft loss events (17 of 20) in the SRL conversion cohort occurred in the first 600 days, whereas in the CNI continuation cohort, half occurred prior today 600 and half after day 600. With the exception of 1 case of retransplantation in the CNI continuation cohort all graft loss events were deaths (although none of the deaths were due to graft loss).

Similarly, reflecting the fact that all but 1 graft loss event were deaths, the rates of subject survival were 94.9% and 96.7% for the SRL conversion and CNI continuation cohorts, respectively (p=0.299). Again the large majority of the deaths in the SRL conversion cohort occurred within the first 600 days. The numerically lower rate of subject survival for SRL versus CNI treatment demonstrated in this study was partly attributable to the of the deaths of 4 subjects in the SRL conversion cohort who, in violation of the protocol, had either clinical documentation of preexisting malignancy at the time of their enrollment or in whom a malignancy was strongly suspected on the basis of disease recurrence that was diagnosed shortly after randomization.

Analysis of the 12 month data revealed biopsy-confirmed acute rejection rates of 11.7% and 6.1% in the sirolimus conversion and CNI continuation cohorts, respectively, a difference that was statistically significant (p=0.017). For the balance of the study up to 144 months , there was no significant difference between the 2 treatment groups in the rates of biopsy-confirmed acute rejection: 6.4% and 3.3% in the SRL conversion and CNI continuation cohorts, respectively (p=0.104). The large majority of acute rejection events (23/25) in the SRL conversion cohort occurred in the first weeks following conversion from CNIs, as might be anticipated following disruption of stable immunosuppression. In the CNI continuation cohort biopsy confirmed acute rejection events were evenly distributed over the course of the study.

The rates of treatment failure, defined as the occurrence of acute rejection or premature discontinuation of study medication for any reason, were 48.3% and 26.7% for the SRL

conversion and CNI continuation cohorts, respectively, a difference that was statistically significant in the ITT analysis ($p<0.001$). The excess in treatment failure in the sirolimus conversion cohort occurred in the first 12 months after SRL conversion; 126 of the 188 treatment failures in the SRL conversion cohort occurred in the first 360 days and 62 of 188 occurred thereafter. In the CNI continuation cohort, 20 of 56 occurred in the first 360 days and 36 of 56 occurred thereafter. The largest contribution to the difference between the 2 groups came from discontinuation of treatment due to AEs.

Over the course of the entire study, significantly more subjects in the SRL conversion cohort experienced at least 1 TEAE (excluding infections and malignancies) than in the CNI continuation group (99.2% in the SRL conversion cohort vs 95.7% in the CNI continuation cohort; $p = 0.005$).

The overall incidence of infection-related TEAEs was similar between the 2 treatment groups: 69.2% in the SRL conversion cohort versus 61.9% in the CNI continuation cohort ($p<0.084$). However, significantly more subjects in the SRL conversion cohort than in the CNI continuation cohort had TEAEs of hepatitis (2.3% vs 0%; $p= 0.031$), and herpes simplex (8.5% vs 1.4%; $p<0.001$). The clinical significance of the imbalance in Investigator reported hepatitis is unclear as mean HCV RNA titers collected over time in all HCV positive subjects revealed significantly lower titers in the SRL group at Month 3, and numerically lower titers at other timepoints.

There was no significant difference between the 2 treatment groups in the overall incidence of malignancies (12.1% in the SRL conversion group vs 17.1% in the CNI continuation group; $p=0.107$). The incidence of skin carcinomas was significantly lower in the SRL conversion cohort than in the CNI continuation group (3.6% vs 9.0%;$p = 0.008$).

The individual TEAEs that were significantly more frequent in the SRL conversion cohort, including asthenia, fever, headache, diarrhea, mouth ulceration, stomatitis, anemia, leukopenia, thrombocytopenia, hypercholesteremia, hyperlipemia, and peripheral edema. These TEAEs are consistent with the known adverse drug reaction (ADR) profile of SRL, with the exception of asthenia. Of note, among the 607 liver transplant subjects in the study, only 1 case of hepatic artery thrombosis was reported, in a subject in the SRL conversion cohort.

The observed differences between the 2 treatment groups in mean concentrations of the biochemical and hematologic laboratory variables studied in this clinical trial were consistent with the known respective ADR profiles of SRL and the CNIs. In particular, mean fasting lipid concentrations increased significantly following SRL conversion, and remained elevated through study end. Mean serum concentrations for potassium, calcium, and phosphorous were lower in the SRL group, along with hemoglobin, white blood cells, platelets, albumin, urea, and uric acid. Mean serum concentrations for magnesium tended to be higher in the SRL conversion group. None of these observed differences between treatments were of clinical significance. These biochemical and hematologic findings are consistent with the known ADR profile of SRL.

In summary, in the face of little or no deterioration in renal function in subjects on continued immunosuppressive therapy with a CNI, this study failed to achieve its main objective of demonstrating superiority in renal function following conversion from CNI-based to SRL-based immunosuppression in maintenance liver transplant recipients. The safety profile of SRL as observed in this study population was consistent with that recorded in the reference safety information for SRL. No previously unrecognized AEs resulting from treatment with SRL were identified.