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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00369382

PROTOCOL NO.: 0468E7-408-GL (B1741006)

PROTOCOL TITLE: A RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE SAFETY AND EFFICACY OF CONVERSION FROM A CALCINEURIN INHIBITOR TO SIROLIMUS VERSUS CONTINUED USE OF A CALCINEURIN INHIBITOR IN CARDIAC TRANSPLANT RECIPIENTS WITH MILD TO MODERATE RENAL INSUFFICIENCY (Protocol 0468E7-408-GL/B1741006)

Study Centers: Multicenter trial

Study Initiation Date and Primary Completion Date: 18 Sep 2006 to 21 May 2010

Phase of Development: Phase 3b/4

Study Objectives:

The primary objective of the study was to demonstrate the superiority of converting from calcineurin inhibitor (CNI) therapy to sirolimus therapy versus continuing CNI therapy with respect to renal function in cardiac transplant recipients with mild to moderate renal dysfunction.

The secondary objectives of the study were:

- To evaluate the safety of conversion from CNI therapy to sirolimus therapy in this subject population.
- To explore the effect of conversion from CNI therapy to sirolimus therapy on surrogate markers of cardiovascular risk.

METHODS

Study Design: This was a phase 3b/4, open-label, randomized, comparative, multicenter, multinational study in adult cardiac transplant recipients with mild to moderate renal

insufficiency. After screening, eligible subjects were treated for approximately 52 weeks with study drug. Subjects were randomly assigned in a 1:1 ratio to continued use of a CNI (tacrolimus [TAC] or cyclosporine [CsA]) in group I or conversion to sirolimus in group II.

Number of Subjects (Planned and Analyzed): The number of subjects planned for this study was 200: 100 in group I (continued use of a CNI [TAC or CsA]) and 100 in group II (conversion to sirolimus). A total of 116 subjects were correctly randomized into the study, 59 subjects were assigned to group I (CNI group) and 57 subjects were assigned to group II (sirolimus group).

Diagnosis and Main Criteria for Inclusion: The main criteria for inclusion in this study included: cardiac transplant recipients aged ≥ 18 years who were receiving CsA or TAC as part of the maintenance immunosuppressive regimen since the time of transplantation, and were ≥12 months after cardiac transplantation but ≤ 96 months after transplantation at the time of screening, with a glomerular filtration rate (GFR) > 40 but < 90 mL/min/1.73m^2 (calculated by the Cockcroft-Gault equation and adjusted for body surface area [BSA] using the Mosteller formula) with stable renal function (defined by having no decrease in GFR > 20%) over the previous 3 months, and left ventricular ejection fraction by echocardiogram (ECHO) ≥ 40%. Key exclusion criteria included treatment of acute rejection within 3 months and spot urine protein:creatinine ratio >0.5 or proteinuria >500 mg/day.

Study Treatment: Subjects assigned to sirolimus were provided 1-mg and 2-mg oral tablets for up to 52 weeks. Subjects were assigned to continued use of a CNI (TAC or CsA) for up to 52 weeks.

Efficacy Evaluations:

The primary efficacy endpoint was change from baseline calculated creatinine clearance (using the Cockcroft-Gault equation and adjusted for body surface area (BSA) using the Mosteller formula) at 52 weeks.

The secondary efficacy endpoints included:

1. Change from baseline in calculated creatinine clearance (using the Cockcroft-Gault equation and adjusted for BSA using the Mosteller formula) at 4, 16, 24, 32, and 40 weeks post-randomization.

2. Change from baseline in calculated creatinine clearance (using the simplified modification of diet in renal disease [MDRD] equation at 4, 16, 24, 32, 40, and 52 weeks post-randomization.

3. Change in serum creatinine level from baseline to 4, 16, 24, 32, 40, and 52 weeks post-randomization.

4. Slope of creatinine clearance (between baseline and 52 weeks).

5. Subject survival.

6. Incidence and severity of biopsy-confirmed acute rejection (BCAR).

7. Time from randomization to first BCAR.

8. Frequency of antibody use in the treatment of acute rejection.

9. Frequency of subjects in group II (CNI conversion to sirolimus) requiring conversion back to CNI therapy.

Safety Evaluations: The safety of sirolimus was determined using the following assessments: monitoring of adverse events (AEs), withdrawal due to AEs, concomitant medications, laboratory determinations (hematology, blood chemistry, fasting lipid profiles, levels of serum creatinine and blood urea nitrogen, and both spot and 24-urine collections of protein and creatinine), vital signs (sitting blood pressure and pulse), standard 12-lead electrocardiograms (ECGs), physical examinations, weight measurements, cardiac biopsy, and survival.

Statistical Methods: The primary endpoint, the change from baseline creatinine clearance at 52 weeks, was compared between treatment groups with an analysis of covariance (ANCOVA) with baseline creatinine clearance as a covariate and treatment group and center as factors. The primary analysis was done on the intent-to-treat (ITT) population (all subjects randomized into the study). Both on-therapy and off-therapy values were used. Last observation was carried forward for data points which were missing due to skipped visits and subject dropouts. If none of the post-randomization values were available, the baseline value was carried forward. Data were also summarized for the on-therapy population (all subjects who remained on assigned therapy up to the point they discontinued from assigned therapy) and the safety population (all randomized subjects who received at least 1 dose of study medication).

RESULTS

Subject Disposition and Demography:

Table 1 summarizes the conclusion status of subject participation and primary reasons for discontinuation from the assigned treatment regimen. Table 2 summarizes the conclusion status of subject participation (either on-therapy or off-therapy) and primary reasons for discontinuation from all study participation. A summary of the subject demography for the ITT population is presented in Table 3. The mean time since transplant was 3.9 years (range, 1.1 to 7.7 years)

Table 1: Summary of Conclusion of Subject Participation – End of Treatment – Safety Population

		Treatment		
Conclusion Status Reason	**p-value**	**SRL n=57** n (%)	**CNI n=57** n (%)	**Total n=114** n (%)
Total		57 (100)	57 (100)	114 (100)
Completed	0.003**	33 (57.9)	48 (84.2)	81 (71.1)
Phase Completed	0.003**	33 (57.9)	48 (84.2)	81 (71.1)
Discontinued	0.003**	24 (42.1)	9 (15.8)	33 (28.9)
Adverse Event	<0.001***	19 (33.3)	0	19 (16.7)
Investigator Request	1.000	2 (3.5)	3 (5.3)	5 (4.4)
Other[b]	1.000	1 (1.8)	0	1 (0.9)
Protocol Violation[c]	1.000	1 (1.8)	0	1 (0.9)
Subject Request	0.113	1 (1.8)	6 (10.5)	7 (6.1)

Abbreviations: SRL=sirolimus; CNI=calcineurin inhibitor; n=number of subjects; ITT=intent-to-treat
[a.] Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
[b.] Other reason for discontinuation was sudden death.
[c.] Protocol violation was sirolimus discontinued >10 days.
Overall P-Value: Fisher's Exact Test P-value (2-Tail).
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
The 2 subjects in the ITT population, who were not in the safety population are not included here since they never received treatment.

Table 2: Summary of Conclusion of Subject Participation – Study – Safety Population

		Treatment		
Conclusion Status Reason[a]	**Overall P-Value**	**SRL n=57 n (%)**	**CNI n=57 n (%)**	**Total n=114 n (%)**
Total	1.000	57 (100)	56 (98.2)[b]	113 (99.1)
Completed	0.203	54 (94.7)	49 (86.0)	103 (90.4)
Study Completed	0.203	54 (94.7)	49 (86.0)	103 (90.4)
Discontinued	0.321	3 (5.3)	7 (12.3)	10 (8.8)
Death	0.496	2 (3.5)	0	2 (1.8)
Investigator Request	1.000	1 (1.8)	2 (3.5)	3 (2.6)
Subject Request	0.057	0	5 (8.8)	5 (4.4)

Abbreviations: SRL=sirolimus; CNI=calcineurin inhibitor; n=number of subjects; ITT=intent-to-treat
[a.] Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
[b.] One subject (CNI group) was considered lost to follow-up because the site closed before complete conclusion data was obtained. This subject is not included in this table.
Overall P-Value: Fisher's Exact Test P-value (2-tail).
The 2 subjects in the ITT population who were not in safety population are not included here since they never received treatment.

Table 3: Demographic Characteristics of the ITT Population

Characteristic	P-Value	Treatment SRL (n = 57)	Treatment CNI (n = 59)	Total (n = 116)
Age, years				
Mean	0.348 [a]	57.40	58.93	58.18
Standard Deviation		9.42	8.01	8.73
Sex, N (%)	0.055 [b]			
Female		12 (21.05)	5 (8.47)	17 (14.66)
Male		45 (78.95)	54 (91.53)	99 (85.34)
Race, N (%)	0.779 [b]			
Black or African American		1 (1.75)	2 (3.39)	3 (2.59)
Other		2 (3.51)	3 (5.08)	5 (4.31)
White		54 (94.74)	54 (91.53)	108 (93.10)
Height (cm)				
N		56	59	115
Mean	0.870 [a]	172.40	172.13	172.26
Standard Deviation		9.96	8.11	9.02
Missing		1	0	1
Weight (kg)				
Mean	0.968 [a]	81.97	81.86	81.91
Standard Deviation		14.44	15.34	14.84

Abbreviations N/n=number of subjects; cm=centimeter; kg=kilogram; SRL=sirolimus; CNI=calcineurin inhibitor; ITT-intent-to-treat

[a] One-way analysis of variance with Treatment as factor.

[b] P-value for Chi-Square.

Efficacy Results:

The results of ANCOVA analysis of calculated creatinine clearance (Cockcroft-Gault) at screening, 24 weeks, and 52 weeks on the ITT population are given in Table 4.

Table 4: Analysis of Calculated Creatinine Clearance (Cockcroft-Gault; mL/min/1.73 m^2): ITT Population

Time	Therapy group	Number of Subjects	Mean (SD)	Median	Range (Min-Max)	ADJ Mean CHG (SE)[a]	p-value[b]
Screening	group I	59	57.09(11.96)	54.33	33.95-85.15	.	.
	group II	56	57.75(14.04)	54.75	35.54-101.89	.	.
Week 24	group I	59	56.69(14.15)	53.31	33.95-96.77	-1.91(1.28)	0.012
	group II	56	61.21(17.13)	57.78	32.00-115.01	2.15(1.40)	.
Week 52	group I	59	56.53(12.64)	53.99	33.95-96.77	-1.35(1.18)	0.004
	group II	56	61.37(15.18)	58.85	33.29-102.55	3.03(1.29)	.

Abbreviations: ADJ=adjusted; ANCOVA=analysis of covariance; CHG=value-baseline; CNI=calcineurin inhibitor; group I=CNI based; group II=sirolimus based; SD=standard deviation; SE=standard error; ITT=intent-to-treat; min=minimum; max=maximum

[a] ANCOVA Model: Change from baseline creatinine clearance = Baseline Score + Treatment + center

[b] Between group Comparison

Note: Group II included 56 rather than 57 subjects because 1 subject did not have a height measurement, which was required to calculate creatinine clearance

At week 52, the adjusted mean change from baseline in calculated creatinine clearance (Cockcroft-Gault) for the ITT population was significantly higher in the sirolimus group than in the CNI group. This was also observed at week 24. Similar results were observed when using calculated creatinine clearance by MDRD.

At all timepoints (weeks 4, 8, 16, 24, 32, 40, and 52), the adjusted mean changes from baseline in the calculated creatinine clearance (Cockcroft-Gault) for the on-therapy population were significantly higher in the sirolimus group compared with the CNI group. Similar results were observed when using calculated creatinine clearance by MDRD.

At weeks 4, 8, 16, 24, 32, and 52, the adjusted mean change from baseline in serum creatinine was significantly lower in the sirolimus group when compared with the CNI group.

The annual change in calculated creatinine clearance (Cockcroft-Gault) was -0.740 mL/min/1.73 m^2 for group I (CNI group) and 1.571 mL/min/1.73 m^2 for group II (sirolimus group) for the ITT population. Neither of the annual changes in calculated creatinine clearance (Cockcroft-Gault) differed statistically from 0. There was no statistically significant difference between groups.

The annual change in calculated creatinine clearance (Cockcroft-Gault) was -0.724 mL/min/1.73 m^2 for the CNI group for the on-therapy population. The annual change in calculated creatinine clearance (Cockcroft-Gault) was 3.164 mL/min/1.73 m^2, p=0.015 for the sirolimus group for the on-therapy population. There was a statistically significant difference between groups, in favor of the sirolimus group (p=0.027).

During the conduct of the study, there were 3 reasons for performing an endomyocardial biopsy: for cause, by site protocol, and as mandated by study protocol. A total of 6 subjects (5.26%) had BCAR diagnosed from for cause biopsies (5 [8.8%] subjects in the sirolimus group and 1 [1.8%] subject in the CNI group; p=0.206). Twenty-two subjects underwent site-protocol biopsies (11 were in each group); 2 subjects (18.2%) in the sirolimus group had rejection. By protocol, all subjects randomized to the sirolimus group were required to have a biopsy 2-6 weeks after conversion. Of the 39 subjects who had a protocol-required biopsy in the sirolimus group, 7 subjects (18.0%) had rejection. Of the 15 subjects who received treatment for rejection, all received an increased dose of corticosteroids, and 1 subject in the CNI group also received antilymphocyte antibody therapy. Time from randomization to first BCAR was not summarized as planned because the actual start date of rejection was unknown for those diagnosed by site protocol and protocol-required biopsy.

Data on biopsy results was captured using the 1990 International Society for Heart and Lung Transplantation (ISHLT) criteria; however, the severity of acute rejection is summarized in Table 5 using the revised 2005 ISHLT criteria. In each category of rejection, the biopsies considered positive for rejection were categorized according to the following:

- 1990 grade 0 = 2005 grade 0R
- 1990 grades 1A, 1B, and 2 = 2005 grade 1R
- 1990 grade 3A = 2005 grade 2R
- 1990 grades 3B and 4 = 2005 grade 3R.

Table 5: Severity of Rejection Using ISHLT Criteria

Rejection Category	Treatment		
	SRL n=57	CNI n=57	Total n=114
Grade 2R			
Protocol mandated	6	n/a	6
For cause	4	0	4
Site protocol	1	0	1
Grade 3R			
Protocol mandated	1	n/a	1
For cause	1	1	2
Site protocol	1	0	1

Abbreviations: CNI=calcineurin inhibitor; n=number of subjects; SRL=sirolimus; n/a=not applicable; ISHLT=International Society for Heart and Lung Transplantation
2005 ISHLT criteria used.

Of the 57 subjects in the sirolimus group, 21 were converted back to a CNI; 11 (19.3%) were converted to CsA and 10 (17.5%) were converted to TAC.

Safety Results:

Treatment-emergent AEs (TEAEs) reported by greater than or equal to 10% of the subjects in any group are summarized by treatment group in Table 6.

Table 6: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events With an Incidence of Greater Than or Equal to 10% in Any Treatment Group – Safety Population

		Treatment		
Body System[a] Adverse Event	**p-value**	**SRL n=57 n(F)=12 n(M)=45**	**CNI n=57 n(F)=5 n(M)=52**	**Total n=114 n(F)=17 n(M)=97**
Any Adverse Event	<0.001***	55 (96.5)	40 (70.2)	95 (83.3)
Body as a Whole	<0.001***	39 (68.4)	18 (31.6)	57 (50.0)
Abdominal Pain	0.361	8 (14.0)	4 (7.0)	12 (10.5)
Headache	0.094	8 (14.0)	2 (3.5)	10 (8.8)
Cardiovascular System	0.055	20 (35.1)	10 (17.5)	30 (26.3)
Hypertension	0.162	7 (12.3)	2 (3.5)	9 (7.9)
Digestive System	<0.001***	37 (64.9)	16 (28.1)	53 (46.5)
Aphthous Stomatitis	0.006**	8 (14.0)	0	8 (7.0)
Diarrhea	0.031*	16 (28.1)	6 (10.5)	22 (19.3)
Mouth Ulceration	0.027*	6 (10.5)	0	6 (5.3)
Hemic and Lymphatic System	<0.001***	16 (28.1)	2 (3.5)	18 (15.8)
Anemia	0.027*	6 (10.5)	0	6 (5.3)
Metabolic and Nutritional	0.004**	30 (52.6)	14 (24.6)	44 (38.6)
Hypercholesteremia	0.113	6 (10.5)	1 (1.8)	7 (6.1)
Hyperlipemia	0.113	6 (10.5)	1 (1.8)	7 (6.1)
Peripheral Edema	0.077	18 (31.6)	9 (15.8)	27 (23.7)
Musculoskeletal System	0.186	17 (29.8)	10 (17.5)	27 (23.7)
Arthralgia	0.271	6 (10.5)	2 (3.5)	8 (7.0)
Nervous System	0.288	18 (31.6)	12 (21.1)	30 (26.3)
Respiratory System	0.151	21 (36.8)	13 (22.8)	34 (29.8)
Cough Increased	1.000	5 (8.8)	6 (10.5)	11 (9.6)
Dyspnea	1.000	7 (12.3)	6 (10.5)	13 (11.4)
Skin and Appendages	<0.001***	34 (59.6)	7 (12.3)	41 (36.0)
Acne	0.006**	8 (14.0)	0	8 (7.0)
Rash	<0.001***	16 (28.1)	2 (3.5)	18 (15.8)
Special Senses	0.361	8 (14.0)	4 (7.0)	12 (10.5)

Abbreviations: CNI=calcineurin inhibitor; F=female; M=male; n=number of subjects; SRL=sirolimus; Transplant rejection is not included in this table.
[a] Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.
Overall P-Value: Fisher's Exact Test P-value (2-Tail).
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.

Major Adverse Cardiac Events (MACE), Malignancy, and Infections

A summary of the number (%) of subjects with major adverse cardiac events is provided in Table 7. A summary of the number (%) of subjects reporting treatment-emergent AEs of

malignancy is provided in Table 8. A summary of number (%) subjects reporting treatment-emergent AEs of infection is provided in Table 9.

Table 7: Number (%) of Subjects With Major Adverse Cardiac Events – Safety Patients

Body System [a.] Adverse Event	p-value	Treatment SRL n=57	CNI n=57	Total n=114
Any Adverse Event	0.679	4 (7.0)	2 (3.5)	6 (5.3)
Cardiovascular System	1.000	2 (3.5)	1 (1.8)	3 (2.6)
Cerebrovascular Accident	1.000	1 (1.8)	0	1 (0.9)
Congestive Heart Failure	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Other treatment	1.000	2 (3.5)	1 (1.8)	3 (2.6)
Insertion of Permanent Pacemaker	0.496	2 (3.5)	0	2 (1.8)
Percutaneous Coronary Intervention	1.000	0	1 (1.8)	1 (0.9)

Abbreviations: SRL=sirolimus; CNI=calcineurin inhibitor; n=number of subjects
[a.] Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.
Overall P-Value: Fisher's Exact Test P-value (2-Tail).

Table 8: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events – Malignancy – Safety Patients

Body System [a.] Adverse Event	p-value	Treatment SRL n=57	CNI n=57	Total n=114
Any Adverse Event	1.000	5 (8.8)	4 (7.0)	9 (7.9)
Digestive System	1.000	1 (1.8)	0	1 (0.9)
Gastrointestinal carcinoma	1.000	1 (1.8)	0	1 (0.9)
Skin and Appendages	1.000	4 (7.0)	4 (7.0)	8 (7.0)
Skin carcinoma	1.000	4 (7.0)	4 (7.0)	8 (7.0)

Abbreviations: SRL=sirolimus; CNI=calcineurin inhibitor; n=number of subjects
[a.] Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.
Overall P-Value: Fisher's Exact Test P-value (2-Tail).

Table 9: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events – Infection – Safety Patients

Body System [a.] Adverse Event	p-value	Treatment SRL n=57	CNI n=57	Total n=114
Any Adverse Event	0.032*	27 (47.4)	15 (26.3)	42 (36.8)
Body as a Whole	0.203	8 (14.0)	3 (5.3)	11 (9.6)
Cellulitus	1.000	0	1 (1.8)	1 (0.9)
Flu Syndrome	1.000	1 (1.8)	2 (3.5)	3 (2.6)
Infection	0.057	5 (8.8)	0	5 (4.4)
Moniliasis	1.000	1 (1.8)	0	1 (0.9)
Sepsis	1.000	1 (1.8)	0	1 (0.9)
Cardiovascular System	1.000	1 (1.8)	0	1 (0.9)
Endocarditis	1.000	1 (1.8)	0	1 (0.9)
Digestive System	0.679	4 (7.0)	2 (3.5)	6 (5.3)
Diarrhea	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Gastroenteritis	1.000	1 (1.8)	0	1 (0.9)
Gingivitis	1.000	1 (1.8)	0	1 (0.9)
Oral Moniliasis	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Vomiting	1.000	1 (1.8)	0	1 (0.9)
Respiratory System	0.828	15 (26.3)	13 (22.8)	28 (24.6)
Bronchitis	1.000	2 (3.5)	1 (1.8)	3 (2.6)
Cough Increased	0.496	2 (3.5)	0	2 (1.8)
Pharyngitis	0.243	3 (5.3)	0	3 (2.6)
Pneumonia	0.118	4 (7.0)	0	4 (3.5)
Sinusitis	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Upper Respiratory Infection	1.000	10 (17.5)	11 (19.3)	21 (18.4)
Skin and Appendages	0.361	8 (14.0)	4 (7.0)	12 (10.5)
Fungal Dermatitis	1.000	1 (1.8)	0	1 (0.9)
Herpes Simplex	0.118	4 (7.0)	0	4 (3.5)
Herpes Zoster	1.000	5 (8.8)	4 (7.0)	9 (7.9)
Special Senses	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Conjunctivitis	1.000	1 (1.8)	0	1 (0.9)
Otitis Externa	1.000	0	1 (1.8)	1 (0.9)
Urogenital System	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Urinary Tract Infection	1.000	1 (1.8)	1 (1.8)	2 (1.8)

Abbreviations: SRL=sirolimus; CNI=calcineurin inhibitor; n=number of subjects
[a.] Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.
Overall P-Value: Fisher's Exact Test P-value (2-Tail).
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.

No subjects from the CNI group (group I) and 2 subjects (3.5%) from the sirolimus group (group II) were withdrawn from all study participation because of AEs. The AEs that caused discontinuation from all study participation were sudden death and pulmonary infection.

There were 2 deaths during the study; both subjects were in the sirolimus group (3.5%). The reasons for death were sudden death and pulmonary infection; both subjects discontinued all study participation due to these events as noted above.

A summary of treatment-emergent SAEs is provided in Table 10.

Table 10: Treatment-Emergent Serious Adverse Events – Safety Population

Body System[a] Adverse Event	p-value	SRL n=57	CNI n=57	Total n=114
Any Adverse Event	0.002**	30 (52.6)	13 (22.8)	43 (37.7)
Body as a Whole	<0.001***	17 (29.8)	3 (5.3)	20 (17.5)
Abdominal pain	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Asthenia	1.000	1 (1.8)	0	1 (0.9)
Fever	1.000	1 (1.8)	0	1 (0.9)
Lab test abnormal	1.000	0	1 (1.8)	1 (0.9)
Sudden death	1.000	1 (1.8)	0	1 (0.9)
Transplant rejection	<0.001***	13 (22.8)	1 (1.8)	14 (12.3)
Cardiovascular System	0.438	5 (8.8)	2 (3.5)	7 (6.1)
Angina pectoris	1.000	0	1 (1.8)	1 (0.9)
Arrhythmia	1.000	1 (1.8)	0	1 (0.9)
Cerebral ischemia	1.000	1 (1.8)	0	1 (0.9)
Endocarditis	1.000	1 (1.8)	0	1 (0.9)
Hypertension	1.000	1 (1.8)	0	1 (0.9)
Hypotension	1.000	1 (1.8)	0	1 (0.9)
Pericardial effusion	1.000	1 (1.8)	0	1 (0.9)
Sick sinus syndrome	1.000	1 (1.8)	0	1 (0.9)
Syncope	1.000	0	1 (1.8)	1 (0.9)
Digestive System	0.742	6 (10.5)	4 (7.0)	10 (8.8)
Biliary pain	1.000	1 (1.8)	0	1 (0.9)
Cholelithiasis	0.496	0	2 (3.5)	2 (1.8)
Constipation	1.000	0	1 (1.8)	1 (0.9)
Diarrhea	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Gastroenteritis	1.000	1 (1.8)	0	1 (0.9)
Gastrointestinal carcinoma	1.000	1 (1.8)	0	1 (0.9)
Gastrointestinal disorder	1.000	1 (1.8)	0	1 (0.9)
Liver function tests abnormal	1.000	1 (1.8)	0	1 (0.9)
Rectal hemorrhage	1.000	1 (1.8)	0	1 (0.9)
Hemic and lymphatic system	1.000	1 (1.8)	0	1 (0.9)
Anemia	1.000	1 (1.8)	0	1 (0.9)
Musculoskeletal system	0.618	3 (5.3)	1 (1.8)	4 (3.5)
Arthrosis	1.000	0	1 (1.8)	1 (0.9)
Myalgia	0.243	3 (5.3)	0	3 (2.6)
Nervous system	1.000	1 (1.8)	0	1 (0.9)
Confusion	1.000	1 (1.8)	0	1 (0.9)
Respiratory system	0.094	8 (14.0)	2 (3.5)	10 (8.8)
Bronchitis	1.000	1 (1.8)	0	1 (0.9)
Dyspnea	1.000	1 (1.8)	1 (1.8)	2 (1.8)
Pharyngitis	1.000	1 (1.8)	0	1 (0.9)
Pneumonia	0.118	4 (7.0)	0	4 (3.5)
Upper respiratory infection	1.000	2 (3.5)	1 (1.8)	3 (2.6)
Skin and appendages	0.679	2 (3.5)	4 (7.0)	6 (5.3)
Herpes zoster	1.000	0	1 (1.8)	1 (0.9)
Skin carcinoma	1.000	2 (3.5)	3 (5.3)	5 (4.4)

Abbreviations: SRL=sirolimus; CNI=calcineurin inhibitor; n=number of subjects
Events of 'transplant rejection' may include any grade of rejection regardless of clinical significance.
[a] Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.
Overall P-Value: Fisher's Exact Test P-value (2-Tail).
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.

There were no statistically significant differences between groups in the change from baseline to week 52 in mean fasting HDL or triglycerides. There were statistically significant mean changes from baseline to week 52 in mean fasting LDL and total cholesterol/lipid values, with higher mean increases from baseline in sirolimus subjects.

Although the overall use of anti-hyperlipidemic medications was not different between the 2 groups (96.5% in the sirolimus group vs 91.2% in the CNI group, $p>0.05$), more subjects in the sirolimus group required new/additional anti-hyperlipidemic medications during the study (22.8% in the sirolimus group vs 7.0% in the CNI group, $p=0.033$).

There were no other important differences between groups in clinical laboratory or vital signs data.

CONCLUSIONS:

Cardiac transplant recipients are at risk for development of chronic renal failure related to CNI nephrotoxicity. Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, does not exhibit nephrotoxic effects similar to that of CNIs. Therefore, the rationale of this study was to compare the effect of conversion from a CNI to sirolimus versus continued CNI therapy with respect to renal function in cardiac transplant recipients with mild to moderate renal insufficiency.

Subjects enrolled in this study were adult cardiac transplant recipients who were between 1 to 8 years post-transplant, receiving a CNI-based immunosuppressive regimen since the time of transplant and had mild to moderate renal insufficiency (estimated GFR [eGFR] >40 but <90 mL/min/1.73 m^2). Of the 121 subjects enrolled and randomized, 5 were randomized in error; the remaining 116 subjects had a mean age of 58 years and were an average of 3.9 years post-transplant. There was a significantly higher rate of treatment discontinuations in the sirolimus group (42.1% vs 15.8%, $p=0.003$), primarily due to AEs (33.3% vs 0%, $p<0.001$). This observed higher rate of treatment discontinuations was anticipated in part due to a major change being made, after a significant time post-transplant, to the immunosuppressive regimen in subjects randomized to sirolimus as opposed to those relatively stable subjects randomized to CNI. Despite this, most subjects continued to be followed for the duration of the 1 year study (sirolimus group [94.7%], CNI group [86%]; $p=0.203$).

The adjusted mean change from baseline in creatinine clearance (Cockcroft-Gault) at 1 year was significantly different between groups ($p=0.004$): the sirolimus group increased 3.0 mL/min/1.73 m^2 from baseline, and the CNI group decreased 1.4 mL/min/1.73 m^2 from baseline (ITT). Results in the on-therapy population were similar to the ITT population. The results of eGFR (by MDRD equation) and serum creatinine were consistent with the results of the primary endpoint. The treatment group difference was observed early at week 4, which may be related to hemodynamic effects, although the difference was maintained at 1 year. The slope of estimated creatinine clearance between baseline and 52 weeks (ie, annual change in creatinine clearance) was 3.2 mL/min/1.73 m^2 in the sirolimus group and -0.724 mL/min/1.73 m^2 for the CNI group ($p=0.027$, on-therapy population).

During the conduct of the study, there were 3 reasons for performing an endomyocardial biopsy: for cause, by site protocol and as mandated by study protocol. It is important to note that study protocol biopsies were mandated only for those subjects randomized to the sirolimus group as many investigators had felt that it would not be ethical to require a biopsy in the CNI group in which there had been no change to their immunosuppressive regimen creating a likely bias to identify cases of subclinical rejection in subjects in the sirolimus group. Therefore, the rejection data are reported by reason for biopsy. There were 7 subjects with rejection of the 39 subjects with protocol mandated biopsies in the sirolimus group (18.0%). By biopsies for cause or by site protocol, the rates of acute rejection were not significantly different between groups, although there was an observed trend toward a numerically higher rate in the sirolimus group. There were 2 events of acute rejection that were associated with hemodynamic compromise, 1 in each group.

TEAEs were reported more frequently in subjects in the sirolimus group (96.5% vs 70.2%. $p<0.001$). The following TEAEs occurred statistically significantly more frequently in the sirolimus group: aphthous stomatitis/mouth ulceration, diarrhea, anemia, acne and rash. There were more infections in the sirolimus group (47.4% vs 26.3%, $p=0.032$). There was no significant difference in the incidence of malignancies or major cardiac adverse events (MACE) between groups. Overall higher rates of TEAEs in the sirolimus group were anticipated again given the major change in their immunosuppressive regimen and the timing post-transplant. As previously stated, there were more discontinuations from assigned therapy due to AEs in the sirolimus group. The AEs that most frequently caused discontinuation from therapy were transplant rejection (7 subjects) and pneumonia (2 subjects). There were 2 deaths (sudden death and pulmonary infection) reported during the study, both in the sirolimus group. With regards to the laboratory data, total cholesterol was significantly higher in the sirolimus group than in the CNI group; additionally, more subjects in the sirolimus group required new/additional anti-hyperlipidemic medications.

In summary, conversion from a CNI to sirolimus in cardiac transplant recipients with mild to moderate renal insufficiency resulted in better renal function when compared to those who remained on CNI therapy, as demonstrated by the adjusted mean change from baseline in creatinine clearance through 1 year. However, there was an attendant risk of acute rejection with a trend for a numerically higher rate observed in the subjects converted to sirolimus. There was also a significantly higher rate of discontinuations due to AEs, although the AEs observed in this trial were consistent with the known safety profile of sirolimus. Therefore, for cardiac transplant recipients with mild to moderate renal dysfunction, conversion from a CNI to sirolimus may be a potential treatment option although the potential benefits and risks must be considered for each individual patient.