

Table 7

The principal etiologies of renal failure in patients enrolled in study 301 (%)

Disease	SRL 2 (n=284)	SRL 5 (n=274)	Azathioprine (n=161)
Autoimmune	13 (5)	7 (3)	13 (8)
Diabetes mellitus	59 (21)	53 (19)	32 (20)
Glomerulonephritis	64 (23)	50 (18)	18 (11)
Hypertension	72 (25)	77 (28)	47 (29)
IgA nephropathy	12 (4)	12 (4)	7 (4)
Interstitial nephritis, pyelonephritis	7 (2)	6 (2)	3 (2)
Obstructive uropathy/reflux	15 (5)	16 (6)	9 (6)
Polycystic kidney disease	23 (8)	32 (12)	19 (12)
unknown	19 (7)	21 (8)	13 (8)

1 Twelve month data is from the Applicant's analysis found in the Advisory Committee Briefing Package dated 7/27/99.

Protocol Violations

There were no systematic deviations from the protocol, in this study, which impacted on the outcome. Six patients did not receive their first dose of study medication within the 24-48 hour window after transplantation, as dictated by the protocol. Several patients received one or more doses of open-label azathioprine during hospitalization and were allowed to stay in the study.

8.1.1.4.2 Efficacy endpoint outcomes

This section reflects discussion with the FDA Statistical Reviewer. For further details, please refer to the Statistical Review dated August 20, 1999.

The primary objectives of study 301 were to evaluate the superiority of sirolimus compared to azathioprine with respect to efficacy failure and to exclude that patient and graft survival were unacceptably impaired, based on the 97.5% confidence intervals of the differences in survival rates. Thus, the co-primary efficacy endpoints were efficacy failure at 6 months, and patient and graft survival at 12 months. Efficacy failure was defined as biopsy proven acute rejection, graft loss or death. Patients lost to follow-up at 6 months were treated as efficacy failures in the primary analysis. There was complete ascertainment of patient and graft survival status at one year.

Tables 8 and 9 summarize overall efficacy failure at 6 months as well as efficacy failure in selected subgroups of particular interest in Study 301.

Table 8
Efficacy Failure at 6 months Study 301¹

	Rapamune® 2 mg/day (n=284)	Rapamune® 5 mg/day (n=274)	Azathioprine (n=161)
Overall rate of efficacy failure, n(%)	53 (18.7)	46 (16.8)	52 (32.3)
Acute rejection	47 (16.5)	31 (11.3)	47 (29.2)
Graft loss	3 (1.1)	8 (2.9)	4 (2.5)
Death	2 (0.7)	5 (1.8)	0
Lost to follow-up	1 (0.4)	2 (0.7)	1 (0.6)
CMH p-value	0.002	0.001	
Relative risk (stratified)	0.61	0.58	
(97.5% CI)	(0.42, 0.88)	(0.39, 0.85)	
Stratified differences in rates	-13.3	-14.6	
(97.5% CI)	(-23.2, -3.4)	(-24.5, -4.7)	

1. FDA analysis

In the primary, intent-to- treat, analysis of study 301 the overall rate of efficacy failures were 18.7% (53/284) for sirolimus 2mg/day, 16.8% (46/274) for sirolimus 5mg/day and 32.3% (52/161) for azathioprine.

Reviewer's Note: Sirolimus 2mg/day and 5mg/day significantly reduced the incidence of efficacy failure compared to azathioprine during the first six months post transplantation.

Table 9
Efficacy Failure at 6 months
Selected subgroups in Study 301¹

Subgroup	SRL 2 mg/day (n=284)	SRL 5 mg/day (n=274)	Azathioprine (n=161)
Recipient Race			
Blacks	22/63 (34.9)	11/61 (18.0)	14/42 (33.3)
Non-blacks	31/221 (14.0) ^c	35/213 (16.4) ^c	36/119 (31.9)
Recipient Gender			
Female	14/76 (18.4)	20/103 (19.4)	17/71 (23.9)
Male	39/208 (18.8) ^c	26/171 (15.2) ^c	35/90 (38.9)
Donor Source			
Cadaver	39/180 (21.7)	28/167 (16.8) ^a	34/119 (28.6)
Living Related	10/86 (11.6) ^c	15/83 (18.1) ^b	14/33 (42.4)
Living Unrelated	4/18 (22.2)	3/24 (12.5)	4/9 (44.4)
Number of HLA mismatches			
0 to 2	12/69 (17.4)	8/69 (11.6)	7/42 (16.7)
3 to 6	41/215 (19.1) ^c	38/205 (18.5) ^c	45/119 (37.8)

a: Comparison with azathioprine statistically significant at less than 0.05.

b: Comparison with azathioprine statistically significant at less than 0.01

c: Comparison with azathioprine statistically significant at less than 0.001.

1. FDA analysis

Randomization in study 301 was stratified by race, black versus non-black. Among blacks the rates of efficacy failure were 34.9% (22/63) for sirolimus 2mg/day, 18.0% (11/61) for sirolimus 5 mg/day and 33.3% (14/42) for azathioprine.

The rates of efficacy failure among living donor recipients was unexpectedly higher than for cadaveric donors, particularly in the control group.

Reviewer's Note: Efficacy failure was slightly higher at 2mg/day but not statistically significantly superior at 5 mg/per day compared to azathoprine in the black population. Pharmacokinetic analyses did not demonstrate that black patients had lower levels of either cyclosporine or sirolimus. Thus, the differences in outcome by race cannot be explained by different exposures to these drugs.

Additional studies are needed to ascertain the factors that contribute to the higher rate of efficacy failure in the black patients who received sirolimus 2 mg/day. The Applicant is recommending that the higher dose of sirolimus 5 mg/day be used in black patients as well as other "high risk" groups. However, the factors that cause this reduced efficacy in black patients do not appear to be related to pharmacodynamic issues. Consequently, any increase in sirolimus or cyclosporine dose must be weighed against the side-effects of these drugs, including but not limited to the problems associated with "over-immunosuppression" and dose-related adverse events.

Among women there were no statistically significant differences in efficacy failure across treatment groups.

In analyses of data from registries of renal transplantation, recipients of cadaver organs are at greater risk for rejection and graft loss compared to recipients of organs from living donors. Though not statistically significant, a larger proportion of subjects received organs from living donors in the sirolimus treatment groups compared to the azathioprine control group. Rates of efficacy failure among living donor organ recipients were significantly decreased in sirolimus treatment groups compared to azathioprine. Rates of efficacy failure for recipients of cadaver organs assigned to treatment with sirolimus 5 mg per day were significantly decreased compared to azathioprine and only marginally decreased at 2 mg per day. Rates of efficacy failure among cadaver organ recipients were not significantly improved for sirolimus 5 mg per day compared to 2 mg per day; however, the numbers of subjects in these subset analyses may have been too small to detect a true difference.

The quality of HLA match between donors and potential recipients of kidney allografts is an important criteria in the UNOS organ allocation system and a predictor of graft survival. Overall, rates of efficacy failure were greater among patients with 3 to 6 HLA mismatches compared to those with 0 to 2 HLA mismatches. Although the former were at greater risk for efficacy failure they did not appear to significantly benefit from sirolimus 5 mg per day compared to 2 mg per day.

Sirolimus 2 mg/day did not appear to convey an advantage with respect to efficacy failure compared to azathioprine among patients with 0 to 2 HLA mismatches, who were at a lower risk for rejection.

Table 10 includes the results of patient and graft survival 12 months after transplantation for each treatment group. Differences between each Rapamune[®] dose and azathioprine were assessed using Fisher's exact test. There were no statistically significant differences in the rate of patient and graft survival for either comparison ($p > 0.674$). The Rapamune[®] 2 mg/day treatment group had a slightly better patient and graft survival rate at 12 months than the azathioprine treatment group. The 97.5% confidence intervals about the difference in patient and graft survival rates include zero. The lower bounds of these confidence intervals are -4.8% and -7.1% for Rapamune[®] 2 mg/day and Rapamune[®] 5 mg/day, respectively. The upper bounds of the confidence intervals for relative risk imply that the risk of graft loss or death with a functioning graft could be as much as 2 to 3 times greater for a patient on either Rapamune[®] dose compared to azathioprine. Patients who died with a functioning graft accounted for approximately 40% of graft losses in the Rapamune[®] treatment groups.

Table 10
Patient and Graft Survival at 12 months Study 301¹

	Rapamune [®] 2 mg/day (n=284)	Rapamune [®] 5 mg/day (n=274)	Azathioprine (n=161)
Patient and Graft survival, n(%)	269 (94.7)	254 (92.7)	151 (93.8)
Graft loss	8	12	8
Death	7	8	2
Fisher's exact p-value	0.674	0.845	
Relative risk	0.85	1.175	
(97.5% CI)	(0.35, 2.07)	(0.51, 2.72)	
Differences in rates	0.9	-1.1	
(97.5% CI)	(-4.8, 6.6)	(-7.1, 4.9)	

1. FDA analysis

Overall patient and graft survival at 12 months in study 301 were 94.7% (269/284) for sirolimus 2mg per day, 92.7% (254/274) for sirolimus 5 mg per day, and 93.8% (151/161) for azathioprine by intent-to-treat analysis. The 97.5% confidence intervals for the differences in patient and graft survival at 12 months (rate for sirolimus minus rate for azathioprine control) were -4.8% to +6.6% for sirolimus 2 mg per day, and -7.1% to +4.9% for sirolimus 5 mg per day.

Reviewer's Note: Patient and graft survival were excellent in both studies and the 97.5% confidence intervals for differences in survival between Rapamune[®] and azathioprine included zero. The overall treatment effects observed on biopsy proven acute rejection were not associated with a detectable improvement in patient or graft survival at one year.

Table 11 includes the results of patient survival 12 months after transplantation for each treatment group. Differences between each Rapamune[®] dose and azathioprine were assessed using Fisher's exact test. The relative risk and difference in rates of patient survival for each comparison are also presented in the table. Both Rapamune[®] groups had more deaths than the azathioprine group. However, there was no statistically significant difference in the rate of patient survival for either comparison ($p > 0.271$). The 97.5% confidence intervals about the difference in survival rates include zero. The lower bounds of these confidence intervals are -4.6% and -6.2% for Rapamune[®] 2 mg/day and Rapamune[®] 5 mg/day, respectively. The upper bounds of the confidence intervals for the relative risk imply that the risk of death could be as much as 6 to 9 times greater for a patient on either Rapamune[®] dose compared to azathioprine.

Table 11
Patient Survival at 12 months Study 301¹

	Rapamune [®] 2 mg/day (n=284)	Rapamune [®] 5 mg/day (n=274)	Azathioprine (n=161)
Patient survival, n(%)	276 (97.2)	263 (96.0)	158 (98.1)
Death	8	11	3
Fisher's exact p-value	0.753	0.271	
Relative risk (97.5% CI)	1.51 (0.34, 6.78)	2.16 (0.51, 9.12)	
Differences in rates (97.5% CI)	-0.9 (-4.6, 2.8)	-2.1 (-6.2, 2.0)	

1. FDA analysis

The first acute rejection episode was classified by the Banff criteria of grade I (mild), grade II (moderate), or grade III (severe) acute rejection. Patients not having efficacy failure were categorized as none and patients who had an outcome of graft failure, death, or lost to follow-up were categorized as other. Treatment differences in histological grade of the first acute rejection episode were assessed through generalized CMH methods (row means score statistic) because of the ordinal nature of the response. Among all randomized patients, there are lower rates of mild, moderate, and severe rejection in the Rapamune[®] groups than in the azathioprine group. For patients who had an acute rejection, the distribution of histological grade of acute rejection is not different between treatment groups. (Please see Table 12).

Table 12
Histological Grade of Acute Rejection at 6 Months Study 301¹

	Rapamune® 2 mg/day (n=284, 47) ^a	Rapamune® 5 mg/day (n=274, 31)	Azathioprine (n=161, 47)
None	231 (81.3, -) ^b	228 (83.2, -)	109 (67.7, -)
Grade I (mild)	21 (7.4, 44.7)	19 (6.9, 61.3)	19 (11.8, 40.4)
Grade II (moderate)	19 (6.7, 40.4)	8 (2.9, 25.8)	23 (14.3, 48.9)
Grade III (severe)	7 (2.5, 14.9)	4 (1.5, 12.9)	5 (3.1, 10.6)
Other	6 (2.1, -)	15 (5.5, -)	5 (3.1, -)

a: Total number of randomized patients, Number of patients with acute rejections

b: # of patients with event (Percent of all randomized patients, Percent of acute rejections)

c: All randomized patients, Acute rejections only

1. FDA analysis

Reviewer's note: *The reduction in the incidence of first biopsy-confirmed acute rejection episodes in Rapamune® treated patients, compared to the control groups, included a reduction in all grades of rejection.*

In study 301, the use of anti-T-lymphocyte antibody therapies to treat the first biopsy-confirmed acute rejection during the first 6 months post-transplant was significantly reduced for sirolimus 5 mg compared to the control groups.

Reviewer's note: *This decrement in the use of anti- T-lymphocyte antibody preparations was a secondary study endpoint and did not translate into improved survival, decreased rate of infection or decreased rate of post-transplant lymphoproliferative disease (PTLD). In fact, the incidence of PTLD was highest in the sirolimus 5 mg study arm.*

8.1.1.4.3 Safety outcomes

The safety population includes all patients who received at least one dose of study drug: SRL 2 (281 patients), SRL 5 (269 patients) and AZA (159 patients).

Most adverse events occurred in the first six months post-transplantation. Additional safety information on cumulative adverse events up to 12 months post-transplantation was submitted in the 90 day safety update (dated March 15, 1999) and in subsequent submissions. No new patterns of adverse events were detected in the safety update. Adverse events were coded according to the COSTART system using the preferred term and body system.

Table 13 Number (%) of Patients Reporting Treatment Emergent Adverse Events (>5%) Study 301 (12 month data)¹

Body system Event	Rapamune® 2 mg/day (n=281)	Rapamune® 5 mg/day (n=269)	AZA (n=160)	p-value*
Body as a whole				
Abdominal Pain	79(28)	81(30)	46(29)	
Asthenia	107(38)	108(40)	59(37)	
Chest Pain	45(16)	51(19)	26(16)	
Arthralgia	69(25)	73(27)	34(21)	
Back Pain	45 (16)	69 (26)	37 (23)	5>2
Chills	24 (9)	28 (10)	8 (5)	
Dysuria	26 (9)	40 (15)	22 (14)	
Edema	68 (24)	43 (16)	37 (23)	
Facial edema	17 (6)	37 (14)	9 (6)	5>2
Fever	76 (27)	90 (33)	52 (33)	
Lymphocele	38 (14)	50 (19)	8(5)	
Scrotal edema	18 (6)	15 (6)	2(1)	
Headache	65(23)	73(27)	34(21)	
Pain	67(24)	78(29)	48(30)	
Cardiovascular system				
Hypertension	122 (43)	104 (39)	46 (29)	
Hypotension	16 (6)	30 (11)	24 (15)	5>2
Tachycardia	35 (12)	46 (16)	8 (5)	
Digestive system				
Diarrhea	90 (32)	112 (42)	44 (28)	5>2
Constipation	79(28)	92(34)	59(37)	
Dyspepsia	48(17)	62(23)	38(24)	
Nausea	87(31)	97(36)	62(39)	
Vomiting	59(21)	67(25)	50(31)	
Hemic and lymphatic system				
Anemia	76 (27)	100 (37)	46 (29)	5>2
Ecchymosis	18 (6)	26 (10)	13 (8)	
LDH increased	31 (11)	37 (14)	13 (8)	
Leukopenia	25 (9)	41 (15)	32 (20)	5>2
Thrombocytopenia	36 (13)	53 (20)	15 (9)	5>2
Thrombotic Thrombocytopenic Purpura(HUS/TTP)	4 (1)	8 (3)	3 (2)	
Metabolic and nutritional				
Cushing's syndrome	21 (7)	24 (9)	2 (1)	
Hypercalcemia	10 (4)	5 (2)	14 (9)	
Hypercholesterolemia	108 (38)	113 (42)	53 (33)	
Hyperkalemia	42 (15)	32 (12)	38 (24)	
Hyperlipemia (triglycerides)	106 (38)	118 (44)	45 (28)	
Hypokalemia	47 (17)	56 (21)	18 (11)	
Creatinine increased	98(35)	100(37)	45(28)	
Hypophosphatemia	56(20)	62(23)	32(20)	
Peripheral Edema	169(60)	172(64)	93(58)	
Weight Gain	59(21)	40(15)	30(19)	
Nervous system				
Insomnia	38(14)	58(22)	28(18)	5>2
Tremor	87(31)	81(30)	45(28)	

Respiratory System			
Asthma	17 (6)	16 (6)	2 (1)
Epistaxis	10 (4)	18 (7)	1 (1)
Upper respiratory infection	57 (20)	64 (24)	20 (13)
Dyspnea	62(22)	75(28)	37(23)
Pharyngitis	48(17)	43(16)	27(17)
Skin and appendages			
Acne	86(31)	54(20)	27(17)
Hirsutism	17(6)	37(14)	5(3)
Rash	35 (12)	34 (13)	9 (6)

1 Twelve month safety data source is from the Applicant's analysis in the Advisory Committee Briefing Package dated 7/27/99 and the label.

*Overall difference among treatment groups, assessed by Fisher's exact test, was significant for Rapamune® 2 mg /day vs 5 mg/day.

Individual pair-wise comparisons were performed for adverse events that were statistically significantly different among treatment groups.

When compared to the azathioprine control group, specific adverse reactions that occurred in >5% of the study 301 patients, that were associated with the administration of Rapamune® at both the 2mg/day or 5 mg/day dose, and that occurred with a significantly higher frequency included: asthma, Cushing's syndrome, hirsutism, hypertriglyceridemia, hypertension, lymphocele, rash, scrotal edema, tachycardia, thrombocytopenia and upper respiratory infection. Compared to the azathioprine control, Rapamune® 2 mg/day had a higher incidence of acne and Rapamune® 5 mg/day had a higher incidence of diarrhea, epistaxis, facial edema, hirsutism, and hypokalemia.

Certain clinically important adverse events were reported more frequently in the 5mg/day Rapamune® treated groups when compared to the 2 mg/day Rapamune® groups and these included: back pain, diarrhea, insomnia, hypotension, facial edema, hirsutism and laboratory abnormalities such as anemia, thrombocytopenia, and leukopenia.

Deaths

The most common reasons for deaths in study 301 were vascular (cardiovascular or cerebrovascular) and infection.

Table 14 Causes of Death for Study 301 at 12 months

Cause of Death 0-12 months	SRL 2 (n=284)	SRL 5 (n=274)	AZA (n=161)
Vascular	3 (1.1)	6 (2.2)	1 (0.6)
Infection	3 (1.1)	2 (0.7)	1 (0.6)
Malignancy	1 (0.4)	0	1 (0.6)
Other	1 (0.4)	3 (1.1)	0
Total	8 (2.8)	11 (4.0)	3 (1.9)

Reviewer's note: *There were no significant differences in the overall death rates by treatment group at 12 months. The number of deaths was infrequent and not unexpected; there was no unusual pattern of disease. (Please see Table 15).*

Table 15 Study 301(12 month data)
Summary of Deaths, Graft Loss, Malignancy, and Life-Threatening Adverse Events

Event	Rapamune® 2 mg/day (n=284)	Rapamune® 5 mg/day (n=274)	Aza (n=161)
Death	8(2.8)	11(4.0)	3 (1.9)
Graft Loss	8(2.8)	12((4.3)	8 (5.0)
Malignancy	2(0.7)	5(1.8)	3 (1.9)
Life-Threatening Adverse Event	8(2.8)	9(3.3)	0

1. FDA analysis

The most common etiology of graft loss was death with a functioning graft and the second most common etiology of graft loss was acute rejection.

The causes of death in study 301 were varied; most deaths were related to infection and cardiovascular events, followed by hemorrhage, pulmonary embolism, cachexia, and multiple organ failure. There were no unusual or unexpected causes or rates of patient death during the 12 month study period.

There were 20 patients on Rapamune® who experienced graft loss during the first twelve months post-transplant. The reasons for graft loss included renal vein or renal artery thrombosis, acute rejection, and acute tubular necrosis. There were no unusual or unexpected causes or rates for graft loss.

Ten patients developed biopsy-proven malignancy during the first twelve months post-transplant. Seven of the ten patients were randomized to the Rapamune® treatment groups. The distribution of malignancies was similar between treatment groups and included melanoma, basal cell and squamous cell carcinoma, adenocarcinoma of the esophagus, testicular carcinoma and several other types of cancer. No unusual or unexpected pattern of malignancy was detected.

Seventeen patients (all in the sirolimus treatment groups) had non-fatal life-threatening adverse events during the first twelve months post-transplant. Events included severe pneumonia due to infection with opportunistic organisms such as PCP, tuberculosis and coccidioidomycosis, TTP/HUS, intestinal perforation and other complications such as CVA, pulmonary embolism and pancreatitis (not associated with triglyceride abnormalities). No unusual or unexpected patterns were detected.

Reviewer's note: *At 12 months there were no significant differences in graft loss across treatment groups. No unusual or unexpected reasons or patterns for malignancy or life-threatening adverse event emerged.*

The life-threatening adverse events only occurred in the sirolimus 2 mg/day and sirolimus 5 mg/day treated patients at both 6 and 12 months post-transplant. There was no significant increase in the number of life-threatening adverse events at the higher dose of sirolimus.

Post-transplant lymphoproliferative disease (PTLD)

The rates of PTLD in this trial were similar to that which has been reported in other trials of immunosuppressive agents.

In study 301, the rates of PTLD at 12 months were:

SRL 2	0.4%
SRL 5	0.7%
AZA	0.6%

***Reviewer's note:** Epstein-Barr virus (EBV) serologies were not collected on patients at study onset. Thus, I can not comment on whether the cases of PTLD were in "high risk" EBV-negative transplant recipients of EBV-positive donor kidneys. The differences in incidence of PTLD, among treatment groups, was not statistically significant. Despite the decreased use of anti-T-lymphocyte antibody in the SRL arms, the highest incidence of PTLD (0.7%) was in the sirolimus 5 mg arm.*

Infection

There was a decreased incidence of CMV in studies 301 and 302 that the Applicant partially attributed to the use of CMV prophylaxis. However, assessment of the degree of CMV donor and recipient mismatch for study 301 demonstrated that the majority of the black and non-black patients in study 301 were not at high risk to develop CMV infection or disease i.e. they were not CMV negative recipients (R-) of CMV positive donor kidneys (D+) i.e. (CMV D+R-).

***Reviewer's note:** The applicant recommends that "high risk patients" be administered the sirolimus 5 mg/day dose. They claim that the black population incurred less side effects/less risk from sirolimus. Please keep in mind that there were only 166 African-American patients in study 301. Regarding complications from cytomegalovirus infection—the African-American patients may have been a low risk population to develop serious CMV infection and serious CMV disease. (Please see Table 16 and 17).*

Table 16 Analysis Black patients with "high risk" to develop serious CMV infection and disease (CMV D+R-) in Study 301¹

Study 301 Treatment Arms	Black Patients in 301	Black patients CMV D+/R- "high risk"	Black Patients with unknown D/R serologic status for CMV
AZA	42	5/42 (11.9%)	4
SRL 2	63	4/63 (6.3%)	4
SRL 5	61	2/61 (3.3%)	3
Total Black patients	166	11/166 (6.6%)	11 (6.6%)

1. FDA analysis

Table 17 Analysis Non-Black patients with "high risk" to develop serious CMV infection and disease (CMV D+R-)¹

Study 301 Treatment Arms	Non-Black Patients in 301	Non-Black patients CMV D+/R- "high risk"	Non-Black patients with unknown serologic status for CMV
AZA	119	21/119 (17.6%)	0
SRL 2	221	55 /221 (25.0%)	3
SRL 5	213	46 /213 (21.6%)	5
Total Non-Black patients	553	122/553 (22.1%)	8 (1.5%)

1. FDA analysis

Reviewer's note: *The Applicant has made the argument that there were less opportunistic infections in the African-American population in study 301 and thus they could better tolerate increased immunosuppression. However, as one can see in the above tables, the percentage of black patients in study 301, who were at high risk to develop CMV infection and disease, was only 6.6%. The non-black patients in study 301 carried a "high risk" of 22.1%. Many different host and epidemiologic factors, as well as the level of immunosuppression, contribute to the development of post-transplant infection. Unless one is able to account for all of these factors, and in light of the fact that by chance the African-American population in this study may have been at a lesser risk for serious CMV infection, it may be premature to conclude that the black population would better tolerate increased doses of sirolimus or cyclosporine.*

Other important points to note regarding infection:

- 1) There was no increase in the rates of sepsis, pyelonephritis, wound infection and pneumonia across treatment groups in studies 301.

- 2) There was no increase in the incidence of opportunistic infection in either of the sirolimus treatment groups compared to the control groups in studies 301 except for a statistically significant higher incidence of mucosal *Herpes simplex (HSV)* in the sirolimus 5 mg group:

SRL 2	4.6%
SRL 5	10.2%
AZA	4.4%

Reviewer's note: *The increased incidence of mucosal herpes simplex is quite unusual considering many of these patients were receiving either acyclovir or ganciclovir prophylaxis for CMV infection. Both of these two antiviral drugs have efficacy against Herpes simplex virus. Please note that the diagnosis of Herpes simplex infection can be problematic in that it was not always confirmed by laboratory tests such as culture.*

- 3) Despite differences between treatment groups, with respect to episodes of acute rejection requiring additional high doses of immunosuppression, there were no significant differences between treatment groups with respect to serious infection.

Hyperlipidemia

Reviewer's note: *The following tables pertain to an analysis of treatment emergent abnormalities in serum cholesterol and triglycerides that developed in transplant recipients in Studies 301. Data was not collected for HDL, LDL or apolipoproteins during Studies 301 and 302. Consequently, the following analysis utilizes a threshold for "normal cholesterol" as < 200 mg/dl and "elevated cholesterol" as ≥ 240 mg/dl. Keep in mind that the National Cholesterol Education Program (NCEP) guidelines for intervention utilizing lipid-lowering agents relies on data that was not available for our review such as LDL values and cardiac risk factors. The threshold values utilized for the triglyceride analysis include a "normal triglyceride" value of <200 mg/dl and "elevated triglyceride" value of ≥ 500 mg/dl.*

The lipid analysis below differs from the Applicant's analysis in that it evaluates a cohort of patients who had normal cholesterol and triglyceride levels prior to initiation of study drug and who developed hyperlipidemia while on study drug. Hyperlipidemia has been identified as a major side-effect with sirolimus and has surfaced in all Phase II and Phase III studies.

Complete data was available, at baseline and at 12 months, for the lipid analysis (cholesterol and triglycerides) for study 301 and thus no major bias should have affected these analyses.

TABLE 18 Study 301 patients who developed hypercholesterolemia on study drug¹

# study 301 patients	Azathioprine	Sirolimus 2mg	Sirolimus 5mg
Total # study patients in each treatment arm	161	284	274
Patients with pre-study chol. <200mg/dl	116/161 (72.1%)	204/284 (71.8%)	195/274 (71.2%)
Patients with normal baseline cholesterol who developed chol. ≥240 mg/dl on study drug	55/116 (47.4%)	131/204 (64.2%)	133/195 (68.2%)
Fisher's exact p-value		0.005	0.0003

1. FDA analysis

Reviewer's note: As seen in Table 18, a large number of patients on azathioprine (47.4%) developed a new problem with elevated cholesterol. However, the number of patients on sirolimus 2 mg (64.2%) and 5 mg (68.2%), who developed a new problem with elevated cholesterol, was significantly greater than the azathioprine control.

TABLE 19 Study 301 patients who developed hypertriglyceridemia on study drug¹

Study 301 patients	AZA	Sirolimus 2 mg	Sirolimus 5 mg
Total # patients in each treatment arm	161	284	274
Patients with pre-study TG <200mg/dl	121/161 (75.2%)	207/284 (72.9%)	229/274 (83.6%)
Patients with normal baseline TG who developed TG >500 mg/dl on study drug	6/121 (5.0%)	30/207 (14.5%)	41/229 (17.9%)
Fisher's exact p-value		0.01	0.0005

1. FDA analysis

Reviewer's note: As seen in Table 19, a number of patients on azathioprine (5.0%) developed a new problem with elevated triglycerides. However, the number of patients on sirolimus 2 mg (14.5%) and 5 mg (17.9%), who developed a new problem with elevated triglycerides, was significantly greater than the azathioprine control.

Table 20 Analysis of the use of lipid-lowering agents Study 301¹

Study 301	AZA	SRL 2 mg	SRL 5 mg
Patients with normal cholesterol pre-study	116	204	195
Patients initiated on lipid -lowering drug	25 (21.6%)	93 (45.6%)	101 (51.8%)
Patients who continued on lipid-lowering drug at 6-12 months	23 (20%)	59 (29%)	69 (35%)

1. FDA analysis

Reviewer's note: In study 301, 21.6% of the AZA patients who had normal cholesterol at study onset, developed hypercholesterolemia and required a lipid-lowering agent. This is compared to 45.6% and 51.8% of the SRL 2 and SRL5 patients who had normal baseline serum cholesterol, developed hypercholesterolemia on study drug and then required a lipid-lowering agent. Once initiated on a lipid-lowering agent, at least 60% of the sirolimus patients still continued on the lipid-lowering agent at 6-12 months post-transplant. The majority of the lipid-lowering agents used were HMG-CoA reductase inhibitors. No cases of rhabdomyolysis were reported for patients concomitantly taking either dose of sirolimus and an HMG-CoA reductase inhibitor.

As seen in the above tables, a significant proportion of patients who entered these trials with normal lipid profiles, and were treated with sirolimus, developed a new problem with either elevated cholesterol and/or elevated triglycerides. The Applicant states that this problem was manageable with diet, exercise, lipid-lowering agents, reduction in corticosteroids and cyclosporine and that there was no evidence of major vascular disease at the end of one year. However, one year is too early to assess the major sequelae of this hyperlipidemia. Please also keep in mind that these patients may carry additional risk factors for heart disease such as family history, diabetes and hypertension. Values for HDL, LDL and the apolipoproteins were not collected during this trial and consequently it was not possible to include these parameters in the assessment of hyperlipidemia. We looked at the potential role of elevated cyclosporine/sirolimus levels contributing to hyperlipidemia, but found no data to substantiate a correlation. There was no significant increase in hyperlipidemia, in this group of patients with normal baseline lipid values, when the higher sirolimus dose was utilized. The demographics showed that non-Black male patients tended more often to develop hypercholesterolemia on sirolimus 2 mg and 5 mg. Non-Black females developed more problems with hypercholesterolemia on azathioprine. If a patient with a normal pre-study cholesterol developed hypercholesterolemia on any study drug and was initiated on lipid lowering therapy, greater than 60% of those patients continued to require the lipid lowering agent at 6-12 months post-transplant.

Post-transplant diabetes mellitus (PTDM)

PTDM was defined as a patient, without a prior history of insulin-dependent diabetes mellitus (IDDM) or non-insulin dependent diabetes mellitus (NIDDM), who requires the

use of insulin for 30 or more consecutive days with less than 5 days of interruption to maintain a normal, fasting blood glucose concentration. As depicted in Table 21, the incidence of PTDM was highest in the SRL 5 group, when compared to SRL 2 and AZA. However, the overall the incidence of PTDM was uncommon in study 301. PTDM occurred more commonly in the black population and this is not unexpected (please see Table 22).

Table 21 Incidence of PTDM in Study 301

Study 301	SRL 2 (n= 182)	SRL 5 (n=177)	AZA (n=98)
% patients who developed PTDM	8 (4.4)	11 (6.2)	2 (2.0)

Table 22 Incidence of PTDM in Study 301 by Race

Study 301 patients who developed PTDM by race	SRL 2		SRL 5		AZA	
	Black (n=40)	Non-Black (n=142)	Black (n=35)	Non-Black (n=142)	Black (n=23)	Non-Black (n=75)
Black	2 (5.0)		4 (11.4)		2 (8.7)	
Non-Black	6 (4.2)		7 (4.9)		0 (0.0)	

Reviewer's note: Overall, the incidence of PTDM was uncommon in study 301. However, despite greater rates of acute rejection requiring the use of additional steroids to treat the episodes of rejection in the control arms, there was no corresponding increase in PTDM. In fact, the incidence of PTDM is greater in the sirolimus 5 mg study arm, noting that there were 8 patients whose status regarding the use of insulin was unclear (2 patients in the azathioprine arm and 6 patients in the sirolimus 5 mg arm). African-Americans had an increased risk to develop PTDM in this study.

Liver function Tests (LFT's)

Please note that information regarding the serologic status of study patients for Hepatitis B or C was not reported in this study. The LFT's that were assessed included alkaline phosphatase, AST, and ALT. Serum bilirubin levels were not collected.

Reviewer's note: Essentially, the percentage of patients who developed elevations of these LFT parameters to 5 and 10 times the upper limit of normal were equally distributed among the study drug groups in study 301. The overall percentage of LFT elevations was small and no significant trends were identified by race or gender.

Renal Function as measured by Nankivell Glomerular Filtration Rate (GFR) and serum creatinine

Reviewer's comment : *Because renal function at one year may be predictive of long term graft function, several analyses (some were post-hoc) using Nankivell GFR and serum creatinine were performed by both the Applicant and the FDA.*

The information available to date, suggests that sirolimus is not intrinsically nephrotoxic, but this data is limited. In particular, preclinical investigations to evaluate the effect of sirolimus on cyclosporine nephrotoxicity, have not been done (please see phase IV commitments). Consequently, it became important to question why was sirolimus effective at preventing acute rejection but, at 12 months, the renal function, as measured by Nankivell GFR was significantly worse when compared to that of AZA and placebo.

It is important to note that investigators were blinded when they made the decision to discontinue study drug because of acute rejection/decreased renal function. Cyclosporine dose/whole blood cyclosporine trough concentrations were similar across treatment groups. However, the mean/median levels of cyclosporine were above the upper limit of the target range. This is unusual and may have reflected investigator uneasiness/concern about the double-blind aspect of the study.

In the following tables, one can see that in black and non-black patients the GFR was better in the group on AZA at 12 months. In the NDA, the Applicant notes that patients on CsA and sirolimus have higher creatinine levels over time when compared to patients treated with full dose CsA in conjunction with placebo or azathioprine. These creatinine levels show a dose relationship with higher levels of creatinine found in patients treated with SRL 5 mg. The Applicant claims that this is mainly due to CsA nephrotoxicity.

Our analysis attempted to include all patients who had a value for creatinine and/or GFR at 12 months whether or not they were currently on study drug. This population remained similar to the overall study population in study 301 with respect to rates of acute rejection, and time to rejection. Please note that despite attempts to minimize bias, 11-14% of the study population was still excluded from this exploratory analysis because of missing data. (Please see Tables 23 and 24).

Table 23 Study 301 GFR Results at 12months (337-393 days)¹

Treatment	N (observed) /N (total)	Mean GFR (cc/min) +/- SD	p-value
Azathioprine	127/161 (78.9%)	65.9 +/- 19	-----
SRL 2 mg	233/284 (82.0%)	57.4 +/- 19.6	0.001
SRL 5 mg	226/274 (82.5%)	55.1 +/- 19.3	0.001

1.FDA analysis.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 24 Study 301 Creatinine at 12 months (337-393 days)¹

Treatment	N(observed)	Mean creatinine mg/dl +/- SD	p-value
Azathioprine	127	1.6 +/- 0.63	
Sirolimus 2	233	2.17 +/- 1.49	0.0001
Sirolimus 5	227	2.09 +/- 1.36	0.0002

1. FDA analysis.

Reviewer's note: In study 301 both GFR and serum creatinine are significantly better in the azathioprine arm at 12 months. The serum creatinine is better for both blacks and non-blacks in the azathioprine arm at 12 months. There is no statistical improvement in the serum creatinine with sirolimus 5 in the African-American population at 12 months.

It became of interest to evaluate the GFR among those who did not experience a rejection episode to see if there was an underlying difference independent of rejection. Because the mean time to acute rejection in the SRL arms was greater than in the AZA and Placebo groups: it became of interest to compare GFR at 12 months in patients who had experienced at least one episode of acute rejection.

Table 25 Study 301 Mean GFR at 12 months (337-393 days)¹

Treatment	N (obs)	Mean (SE) cc/min	p-value
AZA			
Non-rejector	95	67.5 (2.01)	
Rejector	32	61.1 (2.95)	
SRL 2			
Non-rejector	187	60.0 (1.32)	.0019
Rejector	46	46.7 (3.24)	.0010
SRL 5			
Non-rejector	199	56.3 (1.35)	.0001
Rejector	27	45.7 (3.75)	.0019

1. FDA analysis.

Table 26 Study 301 Mean Serum Creatinine at 12 months (337-393 days)¹

Treatment	N (obs)	Mean (SE) mg/dl	p-value
AZA			
Non-rejector	95	1.51 (0.06)	
Rejector	32	1.83 (0.12)	
SRL 2			
Non-rejector	186	1.97 (0.10)	0.0045
Rejector	47	2.97 (0.28)	0.0001
SRL 5			
Non-rejector	201	2.01 (0.10)	0.0018
Rejector	26	2.70 (0.26)	0.0101

1. FDA analysis.

**APPEARS THIS WAY
ON ORIGINAL**

Reviewer's note: In all treatment groups, patients with at least one episode of biopsy-proven acute rejection, had lower mean GFR and higher serum creatinine at 12 months compared to patients without rejection. Among patients with acute rejection, the mean GFR was decreased and mean serum creatinine was increased in patients assigned to SRL vs those assigned to AZA. Among patients without acute rejection, the mean GFR was decreased and mean serum creatinine was increased in patients assigned to the SRL vs those assigned to AZA.

At the request of the FDA, on August 23, 1999, the Applicant submitted results from a small iohexal clearance study that was conducted on a subset of study 301 patients, in order to measure glomerular filtration rate (GFR) at months 1, 2, 12 and 24 post-transplant. At 12 months the following values were noted:

Study 301 Iohexal Clearance	SRL 2 n=27	SRL 5 n=24	AZA n=32
Mean GFR(SE) at 12 months (cc/min)	48.8 (3.4)	43.3 (4.7)	49.7 (8.0)

Reviewer's note: Iohexal clearance is a more accurate method to measure GFR when compared to serum creatinine and calculated Nankivell GFR. However, the numbers of patients in this study were too small and thus no definitive conclusions can be drawn. Nevertheless, it is important to note that the results show that GFR was better for AZA compared to SRL 5 mg, but was not much better than that of SRL 2 mg.

Hemolytic Uremic Syndrome/ Thrombotic Thrombocytopenic Purpura (HUS/TTP)

Table 27 Rate (%) of HUS/TTP at >12 months

Study 301	SRL 2 n=281	SRL 5 n=269	AZA n=161
Percent patients with HUS/TTP	1.4	2.6	1.9

Reviewer's note: The observed rates of HUS/TTP appear to be within the range of that reported in other clinical studies with cyclosporine. Note that the rates of HUS are higher for SRL 5 mg. No patient deaths occurred due to HUS and overall, in both study 301 and 302, only 3 patients (SRL 5 =2, SRL 2 = 1) lost their grafts.

Hematologic

Important points:

APPEARS THIS WAY
ON ORIGINAL

1) Thrombocytopenia was reported as a dose-related reversible decrease in platelet count and was significantly higher in SRL 5 compared to SRL 2 and AZA. The applicant states that there were no platelet counts under $50 \times 10^9/L$ after month 3. Severe thrombocytopenia ($<50 \times 10^9/L$) was rare (0.2%) and although epistaxis was reported in this trial, there was only one episode of epistaxis associated with thrombocytopenia ($<100 \times 10^9/L$).

2) Leukopenia was significantly more frequent with sirolimus 5 mg compared to sirolimus 2 mg per day, but occurred less frequently than the incidence seen with azathioprine. There were no cases of neutropenia (absolute neutrophil count less than 500 per microliter). Leukopenia resolved with discontinuation of study medication. No white blood cell count was less than $1 \times 10^9/L$ (1000 mm^3).

Reviewer's note: *Leukopenia did not appear to be associated with an increased rate of infection in the sirolimus treatment groups.*

Summary of the important safety issues that arose in study 301:

- 1) Hyperlipidemia is a major issue and will need to be closely followed. It is difficult to ascertain exactly what proportion of patients can be successfully treated with diet and exercise vs lipid-lowering therapy. It is difficult to make any specific recommendations regarding management since treatment decisions will depend on LDL values, which were not available in these studies, and on risk factor stratification/modification.
- 2) The decreased GFR and elevated serum creatinine at the end of 12 months in the sirolimus groups is of concern. The Applicant ascribes this to cyclosporine toxicity however, cyclosporine levels were similar across treatment groups. Additional studies will be necessary to resolve this issue.
- 3) It would be inappropriate to conclude that 166 black patients encountered less difficulty with infectious disease complications in this study and had decreased efficacy with SRL 2 mg/day because they are "under-immunosuppressed". Factors that predispose immunosuppressed transplant patients to infection are multiple and encompass more than just the type of immunosuppressive agent that they are receiving. To suggest that "more sirolimus" is better for this subset of patients or to recommend the use of the sirolimus 5 mg/day dose must be considered in light of efficacy differences in previously shown tables and be weighed against the potential consequences of hyperlipidemia and vascular disease.
- 4) Although enrollment of African-American patients in Study 301 was excellent, the overall number may be too small to exclude an unacceptable increase in less common adverse events associated with a 5 mg maintenance dose of sirolimus over the long term.
- 5) When compared to the azathioprine control group, specific adverse reactions that occurred in $>5\%$ of the study 301 patients, that were associated with the administration of Rapamune® at both the 2mg/day or 5 mg/day dose, and that occurred with a significantly higher frequency included: asthma, Cushing's

syndrome, hirsutism, hypertriglyceridemia, hypertension, lymphocele, rash, scrotal edema, tachycardia, thrombocytopenia and upper respiratory infection. Compared to the azathioprine control, Rapamune® 2 mg/day had a higher incidence of acne and Rapamune® 5 mg/day had a higher incidence of diarrhea, epistaxis, facial edema, hirsutism and hypokalemia.

- 6) Certain clinically important adverse events were reported more frequently in the 5mg/day Rapamune® treated groups when compared to the 2 mg/day Rapamune® groups: back pain, diarrhea, insomnia, hypotension, facial edema, hirsutism and laboratory abnormalities such as anemia, thrombocytopenia, and leukopenia.
- 7) Overall, Rapamune® 2 mg/day and 5mg/day are relatively safe.

8.1.1.5 Conclusions Regarding Efficacy Data

- 1) The results of study 301 demonstrate that Rapamune® 2 mg/day and 5mg/day significantly reduce the incidence of efficacy failure (first occurrence of biopsy-proven acute rejection, graft loss, or death) compared to azathioprine or placebo control groups during the first 6 months after transplantation.
- 2) Among patients treated with sirolimus, graft survival and patient survival were comparable to those of patients treated with azathioprine. The maximum difference that can be excluded with 97.5% certainty is acceptable.
- 3) For patients considered to be at high risk for rejection, the use of Rapamune® 5 mg/day, rather than Rapamune® 2 mg/day, did not significantly improve the rate of efficacy failure.

8.1.2 Reviewer's Trial # 2; Applicant's protocol 0468E1-302-GL

8.1.2.1. Objective/Rationale

The primary objectives of this study were to compare the safety and efficacy of two dose levels of sirolimus versus placebo control, administered concomitantly with standard immunosuppressive therapy (cyclosporine and corticosteroids) in patients receiving renal allografts.

8.1.2.2 Design

The study was designed as a double-blind, multi-center (34 centers), placebo-controlled study where patients were randomly assigned to receive sirolimus 2 mg/day, sirolimus 5 mg/day or placebo in a 2:2:1 ratio. The study was stratified by two variables i.e. investigator and donor origin (cadaver, living-related and living-unrelated). The time of randomization was immediately before transplantation and the computerized randomization/enrollment (CORE) system of automatic trans-telephonic randomization was used to assign treatment.

Reviewer's note: The time of randomization was different from study 301 and randomization prior to transplantation would be expected to capture more patients with surgical site problems and delayed graft function(DGF).

There were some difficulties in adhering to the time of randomization in study 302. Consequently, 67 of the 576 (12%) study 302 patients were assigned to treatment at one or more days after transplantation—as opposed to being randomized prior to transplantation. The Applicant states that an analysis of the primary endpoint, after these patients were excluded, did not show a difference in the overall results. Consequently, it is doubtful that this will bias the study results.

The objective endpoints for study 302 included two co-primary endpoints, efficacy failure which was a composite endpoint of acute rejection, graft loss (defined as nephrectomy or dialysis for 56 or more consecutive days) or death at 6 months, and patient and graft survival at 12 months.

8.1.2.3. Protocol

This was a phase III, multi-center, placebo-controlled, randomized, double-blind, double-dummy, parallel group study. Neoral®, prednisone and sirolimus placebo were chosen as the comparator regimen and this dual regimen is considered to be acceptable standard treatment for recipients of first kidney graft at most participating centers.

Selection of dose levels for sirolimus 2 mg and 5 mg were the same as for study 301 and were based on results obtained from the phase II renal prophylaxis study (0468-E1-203-GL).

8.1.2.3.1 Population

Study 302 was conducted in the U.S, Europe, Canada and Australia. The Black population was comprised mainly of African-Americans but the numbers of black study patients did not approach the percentage of African-Americans that comprise the U.S. transplant population. Notable exclusions from the protocol included multi-organ transplants, re-transplants, patients with high panel reactive antibody (PRA) and patients who required anti-lymphocyte antibody induction. Thus, patients who represented "high risk" recipients were excluded from the study.

Inclusion and Exclusion criteria were similar to that outlined in study 301.

Removal of Patients From Therapy or Assessment

Patients who discontinued using the study medications for any reason were not replaced. Patients who were randomly assigned but did not receive study medications and patients who received study medications but discontinued using them before the end of the

Month 1	200-400 ng/ml
Month 2-3	200-300 ng/ml
≥ Month 3	150-250 ng/ml

APPEARS THIS WAY
ON ORIGINAL

Reviewer's note: *These cyclosporine target trough levels represent the customary concentrations used for cyclosporine in standard regimens. The target cyclosporine troughs at month 1 were slightly higher for study 302 as the control in this study was placebo which meant that control patients were only maintained on dual therapy. It should also be noted, that the majority of study patients actually maintained target trough levels above the upper bound of the recommended ranges. This may reflect investigator uneasiness with the double-blind aspect of this trial.*

Placebo was administered as a loading dose in a volume equivalent to the sirolimus loading dose (6 mL) and then the maintenance dose was administered in a volume equivalent to the sirolimus maintenance dose (2 mL).

Suspected episodes of acute rejection had to be biopsied, within 48 hours of initiation of anti-rejection therapy, in order to confirm the diagnosis. Initial therapy for all acute rejection was corticosteroids. A cumulative dose of >600 mg of IV Solu-medrol over 3 days, or an equivalent oral corticosteroid preparation, was the recommended treatment. Patients who responded with declining serum creatinine, had their corticosteroids tapered to the pre-rejection dose over 5 days. Patients with severe clinical rejection and a biopsy showing Grade III histology could proceed to anti-lymphocyte antibody preparations before the 3 days of corticosteroid therapy had been completed. Patients whose rejection responded to pulse steroids could continue on study medication. Patients who required anti-lymphocyte antibody therapy had to permanently discontinue study drug. Patients with ATN remained in the study unless anti-lymphocyte antibody therapy was required.

Therapy required during the treatment period

Prophylaxis for *Pneumocystis carinii pneumonia* (PCP) during the first year utilizing Bactrim® or suitable alternative.

Antibacterial prophylaxis against urinary tract infection (UTI) is required for all patients for up to 6 weeks post-transplantation if they can't tolerate Bactrim.®

Cytomegalovirus (CMV) prophylaxis was center-specific and was required in "high risk" CMV negative recipients of CMV positive donor kidneys and recommended for lower risk patients. Prophylactic regimens include oral ganciclovir or oral acyclovir with or without immunoglobulin preparations such as CMVIG or IVIG.

Recommended therapy during the treatment period

Prophylaxis against oral candidiasis for 3 months, utilizing either clotrimazole or nystatin.

Fluconazole was not allowed.

8.1.2.3.3 Statistical considerations

The primary analysis of efficacy failure for each study consisted of comparisons between each dose of Rapamune® and the comparator done by using the Cochran-Mantel-Haenszedl (CMH) statistic stratified by investigator. All patients assigned to treatment were included in this analysis ("Intent to treat" or ITT). Comparisons of each dose of Rapamune® with control therapy were made using the Bonferroni correction to the alpha level. Thus, to maintain an overall probability of type I error of 0.05, an adjusted significance level of 0.025 was used for each comparison. Patients defined as lost to follow-up were scored as efficacy failures, regardless of treatment assignment.

For the purposes of determining sample size, efficacy failure rates at 6 months were estimated to be 18% for Rapamune®-treated patients, and 40% for the placebo control group. The randomization ratio was 2:2:1, Rapamune® 2 mg/day to Rapamune® 5 mg/day and control groups, respectively. For this study, 164 patients were needed in each of the two Rapamune® treatment groups and 82 patients in the placebo control groups, in order to have 90% power to declare a significant difference in each comparison under the conditions described; a minimum total of 420 patients was required. The study eventually enrolled patients beyond the minimum number stated in the protocol in order to ensure that the data from a sufficient number of patients at or above the recommended Rapamune® dose level would be available for the safety analysis.

Reviewer's note: FDA agreed to this increase in patient enrollment. Please see the Statistical Review for further details.

8.1.2.4. Results

APPEARS THIS WAY
ON ORIGINAL

8.1.2.4.1. Patient Disposition/Comparability

Three different populations were defined before unblinding the studies for the determination of efficacy and safety:

- 1) intention to treat
- 2) efficacy sub-population and the
- 3) safety population.

APPEARS THIS WAY
ON ORIGINAL

The primary focus of the efficacy analyses in this package is on the intent-to-treat population; that is all patients who are randomized to therapy.

An analysis of the primary endpoint was also performed on an efficacy subgroup of patients who had taken at least the first five consecutive doses of study medication. The purpose of this analysis was to determine the efficacy of the medication in patients who have had an adequate amount of exposure to study medication ("treatment failure").

Patients who are lost to follow-up in these and subsequent analyses have their endpoints scored as events, regardless of therapy, unless otherwise stated.

The population of patients received at least one dose of study medication was the focus of the safety analyses and this included 1260 of the 1295 randomized study patients for studies 301 and 302. The safety population for study 302 included 218 patients who received Rapamune® 2 mg/day, 208 patients who received Rapamune® 5 mg/day, and 124 patients who received placebo.

Reviewer's note: FDA's primary efficacy analysis was based on the intent-to-treat population. FDA concurred with the choice of safety population. FDA did not perform a "treatment failure" analysis.

Investigators study 302

There were thirty-four U.S. and global investigators/study sites for study 302. Enrollments ranged from 2 patients at Prince Henry Hospital in Australia to 66 patients at Dalhousie Hospital in Halifax, Nova Scotia. Two Italian study sites and one U.S. study site were inspected by FDA and no major problems were identified. These overseas and U.S. study site inspections were not performed "for cause" but were part of routine monitoring of foreign and U.S. clinical sites which contributed a significant proportion of subjects to the study.

Study site 30228 had 21/66 discontinuations (31.8%)

The main reasons for discontinuation of study medication included:

SRL 2 mg (n=7)	4 efficacy failure, 1 adverse event, 1 withdraw consent, non-compliance
SRL 5 mg (n=9)	1 efficacy failure, 4 adverse events, 4 patient request to discontinue
Placebo (n=5)	4 efficacy failure, 1 patient request

Reviewer's note: The reasons for discontinuation at this site were not unusual and did not reflect a low threshold for discontinuing patients. I am uncertain regarding the exact percentage of patients who were unblinded when they discontinued study medication.

Patient Demographics

Study 302 was conducted at 34 centers in Australia, Canada, Europe, and the United States. A total of 576 patients were enrolled in the study and randomized to one of the three treatment groups: 2 mg/day Rapamune® (n=227), 5 mg/day Rapamune® (n=219),

and placebo (n=130). Twenty-six patients were randomized into the study but did not receive at least one dose of study medication (9-Rapamune® 2 mg/day, 11-Rapamune® 5 mg/day, and 6-placebo). The most common reasons for not receiving study medication were the occurrence of ATN or increased creatinine (n=10) and protocol violations (n=10). Please see Table 28 below.

Table 28 Patient Accounting by Treatment Group Study 302

Study 302	SRL 2	SRL 5	Placebo
Patients randomized	227	219	130
Patients enrolled	218	208	124

Reviewer's note: The twenty six (26) study 302 patients, who were randomized but failed to enroll, were included in the six month primary analysis of efficacy and in the twelve month follow-up for patient and graft survival. They were evaluated according to their intent-to-treat assignment.

Over the course of the 12 month treatment period following transplantation, several patients discontinued study medication. Discontinuation was defined as having study drug held for ≥ 21 days. See Table 29 (below) which summarizes the reasons for discontinuation and the numbers of patients who discontinued per treatment assignment for study 302. Patients who discontinued study medication were followed-up at one month for collection of adverse event data and were directed to return for follow-up at months 6, 12, 15, 24, and 28 and 36 to collect data on renal function and patient and graft survival.

Table 29

% Study 302 Patients who discontinued during the treatment phase (12 months)¹

Study 302	SRL 2 (n=227)	SRL 5 (n=219)	Placebo (n=130)	Fisher's exact p- Value
Adverse reaction	23 (10.1)	40 (18.3)	9(6.9)	0.0036
Failed to return	0	0	0	N/A
Other medical event	23 (10.1)	25 (11.4)	14 (10.8)	0.9116
Other non-medical event	4 (1.8)	3 (1.4)	0	0.4407
Patient/subject request	10 (4.4)	19 (8.7)	10 (7.7)	0.1671
Protocol violation	1 (<1)	2(<1)	1 (<1)	0.8391
Unsatisfactory response-efficacy	30 (13.2)	31 (14.2)	31 (23.8)	0.0258
Total	91 (40.1)	120 (54.8)	65 (50.0)	0.0067

¹ Twelve month data is from the Applicant's analysis found in the Advisory Committee Briefing Package dated 7/27/99.

Reviewer's note: Overall, the rates of discontinuation in study 302 were high (40.1-54.8%). The most frequent reason for discontinuation in the Rapamune® 2 mg/day

group (SRL 2) and in the placebo control was unsatisfactory efficacy response. The most frequent reason for discontinuation in the Rapamune® 5 mg/day group (SRL 5) was adverse event and it was significantly higher when compared to both SRL 2 and placebo control. These relatively high rates of discontinuation may reflect investigator uneasiness regarding the double-blind design of the trial. High rates of discontinuation may also impact the evaluation of differences in patient and graft survival and renal function parameters at 12, 24 and 28 and 36 months post-transplant and may drive the study results toward showing equivalence between treatment groups. The Applicant submitted a "line listing" of all discontinuations for study 302 (see "Response to FDA for Information" dated May 13, 1999). I believe the numbers and reasons for study 302 discontinuations listed in Table 29, to be correct.

Table 30

Patient Demographics in Study 302¹

	Rapamune® 2 mg/day	Rapamune® 5 mg/day	Placebo	P-value
# Patients	227	219	130	-
Gender (N)				0.588
Female	79	70	39	
Male	148	149	91	
Age mean (SD)	45.6 (12.3)	45.1 (12.2)	45.9 (13.1)	0.446
min, max	15, 71	17, 68	16, 71	
Race (N)				0.762
Caucasian	172	175	103	
Black	26	27	13	
Asian	10	7	3	
Hispanic	6	2	4	
Australian aborigine	3	1	0	
Other	10	7	7	
Donor Source (N)				0.407
Cadaver	173	174	99	
Living (Related)	39	29	27	
Living (Unrelated)	15	16	4	

1. FDA analysis-See Statistical Review.

Table 30 shows the demographic and baseline characteristics for all randomized patients. There were no statistically significant differences across treatment groups. The majority of the patients were male and Caucasian. The source of the donor allograft was primarily cadaveric. The descriptive variables, gender, race, and donor source were evaluated using CMH tests stratified by investigator. Age was evaluated using ANOVA with treatment and investigator as factors. The majority of Blacks were African-American not African Black.

Reviewer's note: There were no statistically significant differences across treatment groups that would be expected to impact on either drug exposure or the efficacy analysis.