Baseline characteristics

The main etiologies for renal failure were hypertension, diabetes mellitus and glomerulonephritis and this is similar to the etiologies of renal failure in the U.S. population.

Table 31
The principal etiologies of renal failure in patients enrolled in study 302 (%)[1]

Disease	SRL 2 (n=227)	SRL 5 (n=219)	Placebo(n=130)
Autoimmune	7 (3)	8(4)	5 (4)
Diabetes mellitus	28 (12)	34 (16)	17 (13)
Glomerulonephritis	65 (29)	51 (23)	32 (25)
Hypertension	35 (15)	27 (12)	2 (17)
IgA nephropathy	19 (8)	18 (18)	12 (9)
Interstitial nephritis, pyelonephritis	13 (6)	6 (3)	8 (6)
Obstructive uropathy/reflux	14 (6)	17 (8)	6 (5)
Polycystic kidney disease	23 (10)	33 (15)	18 (4)
unknown	23 (10)	25 (11)	10 (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 could have impacted on the outcome. Sixty seven patients were assigned to treatment one or more days after transplantation: 52 patients on the day after transplantation, 14 patients on the second day after transplantation and 1 patient on the third day after transplantation. An analysis of the primary endpoint was done by the Applicant with and without these patients and there was no difference in the overall results and thus it is doubtful that this would bias the study results.

8.1.2.4.2 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 302 were to evaluate the superiority of sirolimus compared to placebo 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 primary efficacy endpoints were efficacy failure at 6 months, 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. Please see Tables 32 and 33.

Analysis Results

Table 32 summarizes the results of the primary endpoint, efficacy failure, for each treatment group at 6 months. The following are included in the table.

1. The overall rates of efficacy failure for each treatment group and the rates for each component of the composite endpoint.
2. The p-value of the CMH statistic stratified by investigator (non-informative centers pooled) used to make treatment comparisons.
3. An estimate of the stratified relative risk and confidence interval about the relative risk. The relative risk is a ratio of the rate of efficacy failure for a dosage of Rapamune® over the rate for placebo, adjusted for investigator. A relative risk <1 signifies that a patient treated with Rapamune® is less likely to have an efficacy failure than a patient treated with placebo.
4. The difference in overall rates of efficacy failure adjusted for investigator and corresponding confidence interval. A difference less than 0 indicates a lower rate of efficacy failure in the Rapamune® group than in the placebo group.

The overall rates of efficacy failure in both Rapamune® treatment groups were significantly lower than the overall rate of efficacy rate in the placebo treatment group at the Bonferroni corrected α-level of 0.025. For both Rapamune® treatment groups, the estimate of the relative risk and corresponding confidence intervals indicate that a patient treated with Rapamune® is less likely to have an efficacy failure at 6 months than a patient who is treated with placebo.

In the primary, intent-to- treat, analysis of study 302 the overall rate of efficacy failures were 30.0% (68/227) for sirolimus 2mg/day, 25.6% (56/219) for sirolimus 5mg/day and 47.7% (62/130) for placebo. Please see Table 32 below.

Table 32
Efficacy Failure at 6 months[1]

	Rapamune® 2 mg/day (n=227)	Rapamune® 5 mg/day (n=219)	PLACEBO (n=130)
Overall rate of efficacy failure, n(%)	68 (30.0)	56 (25.6)	62 (47.7)
Acute rejection	56 (24.7)	42 (19.2)	54 (41.5)
Graft loss	7 (3.1)	8 (3.7)	5 (3.9)
Death	5 (2.2)	6 (2.7)	3 (2.3)
CMH p-value	0.002	0.001	
Relative risk (stratified) (97.5% CI)	0.68 (0.51, 0.91)	0.61 (0.47, 0.81)	
Stratified differences in rates (97.5% CI)	-16.4 (-28.1, -4.6)	-21.4 (-33.1, -9.7)	

1.FDA Analysis

Table 33 summarizes the incidence rates of efficacy failure at 6 months stratified by donor origin (cadaver/living). There is a significant treatment effect for both Rapamune® treatment groups. Patients who received an allograft from either a cadaver or living donor treated with Rapamune® 2 mg/day had lower efficacy failure rates than patients receiving an allograft from a cadaver or living donor treated with placebo (Fisher's exact p=0.043 and 0.002, cadaver and living, respectively). Treatment with Rapamune® 5 mg/day compared to placebo conferred a larger significant treatment effect in patients who received an allograft from a living donor than those who received an allograft from a cadaver donor (Fisher's exact p=0.011 and 0.0002, cadaver and living, respectively). The efficacy failure rate of 61.3% for patients who received an allograft from a living donor treated with placebo is higher than would be expected.

Table 33
Efficacy Failure at 6 months Stratified by Donor Orgin[1]

	Rapamune® 2 mg/day (n=227)	**Rapamune® 5 mg/day (n=219)**	**Placebo (n=130)**
Overall rate of efficacy failure, n(%)	68 (30.0)	56 (25.6)	62 (47.7)
Cadaver	54/173 (31.2)	48/174 (27.6)	43/99 (43.3)
Living	14/54 (25.9)	8 /45 (17.8)	19/31 (61.3)
CMH p-value	0.001	0.001	

1.FDA Analysis

Reviewer's note: In the placebo group the outcome is unexpectedly better in the cadaver group when compared to the living donor group but the overall number of patients in the living donor group is small.

Table 34 includes the results of patient and graft survival 12 months after transplantation for each treatment group. There were no statistically significant differences in the rate of patient and graft survival for either comparison (p>0.366). Both Rapamune® treatment groups had a slightly better patient and graft survival rate at 12 months than the placebo 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 –6.3% and –5.2% 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 1½ times greater for a patient on either Rapamune® dose compared to placebo. Patients who died with a functioning graft accounted for approximately 40% of graft losses in the Rapamune® treatment groups. See Table 34 below.

Table 34
Patient and Graft Survival at 12 months Study 302[1]

	Rapamune® 2 mg/day (n=227)	Rapamune® 5 mg/day (n=219)	Placebo (n=130)
Patient and Graft survival, n(%)	204 (89.9)	199 (90.9)	114 (87.7)
Graft loss	15	11	9
Death	8	9	7
Fisher's exact p-value	0.597	0.366	
Relative risk	0.82	0.74	
(97.5% CI)	(0.41, 1.64)	(0.37, 1.51)	
Differences in rates	2.2	3.2	
(97.5% CI)	(-6.3, 10.7)	(-5.2, 11.6)	

1.FDA Analysis

Reviewer's note: ***The differences in patient and graft survival seen in Table 34 were brought to the attention of the Advisory Committee. The Advisory Committee members agreed that the 97.5% confidence interval for the difference in rates was acceptable. The point estimate is in favor of sirolimus, in study 302, and the 97.5% confidence interval characterizes the amount of uncertainty around that estimate. The committee did not raise any concerns about this amount of uncertainty.***

Table 35 includes the results of patient survival 12 months after transplantation for each treatment group. Both Rapamune® groups had numerically more deaths than the placebo group. However, there was no statistically significant difference in the rate of patient survival for either comparison ($p>0.42$). The 97.5% confidence intervals about the difference in survival rates includes zero. The lower bounds of these confidence intervals are –3.9% and –5.7% 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 death could be as much as 2 to 3 times greater for a patient on either Rapamune® dose compared to placebo. See Table 35 below.

Table 35
Patient Survival at 12 months Study 302[1]

	Rapamune® 2 mg/day (n=227)	Rapamune® 5 mg/day (n=219)	Placebo (n=130)
Patient survival, n(%)	219 (96.5)	208 (95.0)	123 (94.6)
Death	8	11	7
Fisher's exact p-value	0.420	1.0	
Relative risk	0.65	0.93	
(97.5% CI)	(0.21, 2.03)	(0.33, 2.68)	
Differences in rates	1.9	0.4	
(97.5% CI)	(-3.9, 7.7)	(-5.7, 6.5)	

1.FDA Analysis

Reviewer's note: ***These differences in patient survival are reasonably acceptable.***

There was a high drop-out rate from study drug leading to a situation where many patients may have received similar therapy despite different treatment assignments. 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 and 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 placebo 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 36 below.

Table 36
Histological Grade of Acute Rejection at 6 Months Study 302[1]

	Rapamune® 2 mg/day (n=227, 56)[a]	Rapamune® 5 mg/day (n=219, 42)	Placebo (n=130, 54)
None	159 (70.0, -)[b]	163 (74.4, -)	68 (52.3, -)
Grade I (mild)	28 (12.3, 50.0)	24 (11.0, 57.1)	21 (16.2, 38.9)
Grade II (moderate)	24 (10.6, 42.9)	17 (7.8, 40.5)	29 (22.3, 53.7)
Grade III (severe)	4 (1.8, 7.1)	1 (0.5, 2.4)	4 (3.1, 7.4)
Other	12 (5.3, -)	14 (6.4, -)	8 (6.2, -)

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)
1.FDA Analysis

Reviewer' note: ***This was one of several secondary endpoints and analyses. The study was not designed to detect statistically significant differences in severity of rejection. At best, we can conclude that the reduction in the incidence of first biopsy-confirmed acute rejection episodes in the sirolimus-treated patients, compared to placebo control, included a reduction in all grades of rejection.***

Rates of efficacy failure were calculated for the following subgroups: recipient race (black, non-black) recipient gender (female, male), donor source (cadaver, living related, living unrelated), and number of HLA mismatches (0 to 2 mismatches, 3 to 6 mismatches). The efficacy failure rates in these subgroups were compared between treatment groups using Fisher's exact test. It should be noted, however, that this study was not powered to detect a significant treatment difference in the different subgroups and the total number of patients in some of these subgroups was relatively small. Please see Table 37 below.

Table 37
Efficacy Failure at 6 months
Selected subgroups in Study 302[1]

Subgroup	SRL 2 mg/day (n=227)	SRL 5 mg/day (n=219)	Placebo (n=130)
Recipient Race			
Blacks	8/26 (30.8)	9/27 (33.3)	5/13 (38.5)
Non-blacks	60/201 (29.9)[c]	47/192 (24.5)[c]	57/117 (48.7)
Recipient Gender			
Female	27/79 (34.2)	21/70 (30.0)	16/39 (41.0)
Male	41/148 (27.7)[c]	35/149 (23.5)[c]	46/91 (50.6)
Donor Source			
Cadaver	54/173 (31.2)[a]	48/174 (27.6)[b]	43/99 (43.4)
Living Related	14/39 (35.9)	5/29 (17.2)[b]	16/27 (59.3)
Living Unrelated	0/15 (0.0)[b]	3/16 (18.8)	3/4 (75.0)
Number of HLA mismatches			
0 to 2	13/51 (25.5)	10/60 (16.7)	7/30 (23.3)
3 to 6	55/176 (31.3)[c]	46/159 (28.9)[c]	55/100 (55.0)

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

Black patients in both Rapamune® groups had slightly lower efficacy failure rates than black patients treated with placebo. These differences did not reach statistical significance. The incidence rate of efficacy failure is slightly higher for black patients treated with Rapamune® 5 mg/day than black patients treated with Rapamune® 2 mg/day. Non-black patients in both Rapamune® groups had significantly lower efficacy failure rates than non-black patients in the placebo group.

Female patients had numerically lower efficacy failure rates in both Rapamune® groups when compared to the placebo group. Male patients in both Rapamune® groups had significantly lower efficacy rates than male patients in the placebo group.

Patients who received a cadaveric donor organ had significant improvement in efficacy failure rates with either dose of Rapamune® when compared to placebo. Patients in both Rapamune® groups who received a living donor organ had lower efficacy failure rates than patients treated with placebo that received a living donor organ. These differences were only significant in the patients who received a living related donor organ treated with Rapamune® 5 mg/day and patients who received a living unrelated donor organ treated with Rapamune® 2 mg/day. Differences in the other living donor and Rapamune® dose sub-groupings could not be detected because of the small number of patients in these sub-groupings.

Patients with 3 to 6 HLA mismatches had significant improvement with either dose of Rapamune® when compared to placebo. Patients with 0 to 2 HLA mismatches were

small in number and only patients treated with Rapamune® 5 mg/day had numerically lower efficacy failure rates when compared to the placebo group.

Reviewer's note: ***In study 302, all subgroup populations appeared to derive some benefit from the addition of Rapamune®. However, please note that in the living – related and living-unrelated donor analysis for placebo, the rates of efficacy failure appear unexpectedly high (59.3 and 75.0) when compared to the rates in the placebo cadaver group (43.4). Overall, numbers of patients in these subgroups were small and definitive conclusions should not be drawn.***

8.1.2.4.3. Safety outcomes

The safety summary presents treatment-emergent adverse events (TEAEs) including and excluding infections, infection rates, and deaths.

Most adverse events occurred in the first six months post-transplantation and became less frequent over time. 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 90 day safety update. Adverse events were coded according to the COSTART system using the preferred term and body system.

Of the 576 patients enrolled in the study, 550 received at least one dose of study medication and were valid for safety: 218 patients received Rapamune® 2 mg/day, 208 patients received Rapamune® 5 mg/day patients, and 124 patients received placebo.

One or more treatment emergent adverse events (TEAEs) that were not related to infection or malignancy were reported during the on-treatment segment of the study. The most commonly occurring TEAEs during the on-therapy period (reported in >5% of patients in any one treatment group) are summarized by treatment group in Table 38. This is the 12 month database.

Table 38 Number (%) of Patients Reporting Treatment Emergent Adverse Events (>5%) Study 302 (12 month safety data)[1]

Body system Event	Rapamune® 2 mg/day (n=218)	Rapamune® 5 mg/day (n=208)	Placebo (n=124)	p-value*
Body as a whole				
Abdominal Pain	63(29)	75(36)	37(30)	
Asthenia	48(22)	58(28)	35(28)	
Chest Pain	39(18)	50(24)	24(19)	
Arthralgia	55 (25)	64 (31)	22 (18)	
Back Pain	50 (23)	45 (22)	25 (20)	
Chills	14 (6)	32 (15)	13 (10)	5>2
Dysuria	23 (11)	38 (18)	11 (9)	5>2
Edema	44 (20)	38 (18)	18 (15)	
Facial edema	13 (6)	26 (13)	7 (6)	5>2
Fever	51 (23)	71 (34)	44 (35)	5>2
Lymphocele	24 (11)	33 (16)	7(6)	
Scrotal edema	4 (2)	10(5)	2(2)	
Headache	74(34)	71(34)	38(31)	
Pain	72(33)	60(29)	31(25)	
Cardiovascular system				
Hypertension	97 (45)	101 (49)	59 (48)	
Hypotension	12(6)	18 (9)	10(8)	
Tachycardia	25(11)	28(13)	6(5)	
Digestive system				
Diarrhea	54 (25)	72 (35)	33 (27)	
Constipation	78(36)	79(38)	38(31)	
Dyspepsia	50(23)	52(25)	42(34)	
Nausea	55(25)	65(31)	36(29)	
Vomiting	41(19)	52(25)	26(21)	
Hemic and lymphatic system				
Anemia	51 (23)	68 (33)	26 (21)	5>2
Ecchymosis	16 (7)	29 (14)	8 (6)	5>2
LDH increased	26 (12)	41 (20)	8 (6)	5>2
Leukopenia	20 (9)	26 (13)	10 (8)	
Thrombocytopenia	30 (14)	62 (30)	11 (9)	5>2
Thrombotic Thrombocytopenic Purpura(HUS/TTP)	6 (3)	18 (9)	4 (3)	5>2
Metabolic and nutritional				
Cushing's syndrome	17 (8)	17 (8)	15 (12)	
Hypercalcemia	9 (4)	5 (2)	3 (2)	
Hypercholesterolemia	94 (43)	96 (46)	28 (23)	
Hyperkalemia	38 (17)	29 (14)	33 (27)	
Hyperlipemia (triglycerides)	98 (45)	118 (57)	28(23)	5>2
Hypokalemia	23 (11)	36 (17)	11(9)	5>2
Creatinine increased	85(39)	83(40)	47(38)	
Hypophosphatemia	33(15)	40(19)	24(19)	
Peripheral Edema	118(54)	120(58)	60(48)	
Weight Gain	24(11)	17(8)	19(15)	
Nervous system				
Insomnia	29 (13)	29 (14)	10(8)	

Tremor	46(21)	46(22)	24(19)	
Respiratory System				
Asthma	10 (5)	9 (4)	4 (3)	
Epistaxis	16 (7)	25 (12)	2(2)	
Upper respiratory infection	57(26)	48(23)	29(23)	
Dyspnea	52(24)	62(30)	37(30)	
Pharyngitis	35(16)	44(21)	27(22)	
Skin and appendages				
Acne	47 (22)	45 (22)	23 (19)	
Hirsutism	19 (9)	19(9)	11 (9)	
Rash	22 (10)	41 (20)	8 (6)	5>2

1. Twelve month safety data source is from the Applicant analysis found in the Advisory Briefing Package dated 7/27/99.
*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 placebo 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:
epistaxis, hypercholesterolemia, hyperlipemia(elevated triglycerides), increased LDH, tachycardia, and thrombocytopenia.

Compared to the placebo control, Rapamune® 5 mg/day had a higher incidence of anemia, arthralgia, dysuria, ecchymosis, facial edema, fever, hypokalemia, lymphocele, and rash.

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: anemia, chills, dysuria, ecchymosis, facial edema, fever, hyperlipemia (elevated triglycerides), hypokalemia, increased LDH, rash, thrombocytopenia, and TTP/HUS.

Deaths

The causes of death for all treatment groups at 12 months are depicted in Table 39 below. Most deaths were related to infection or vascular events (cardiovascular and cerebrovascular).

Table 39 Causes of Death for Study 302 at 12 months

Cause of Death 0-12 months	SRL 2 (n=227)	SRL 5 (n=219)	Placebo (n=130)
Vascular	3 (1.3)	2 (0.9)	4 (3.1)
Infection	4 (1.8)	4 (1.8)	1 (0.8)
Malignancy	0	2 (0.9)	0
Other	1 (0.4)	3 (1.4)	2 (1.5)
Total	8 (3.5)	11 (3.8)	7 (5.4)

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.***

Table 40 summarizes the number of patients with serious and clinically important adverse events; limited to patient death, graft loss, malignancy and life-threatening adverse events at 6 months.

Table 40 Study 302[1]
Summary of Deaths, Graft Loss, Malignancy, and Life-Threatening Adverse Events

Event	Rapamune® 2 mg/day (n=227)	Rapamune® 5 mg/day (n=219)	Placebo (n=130)
Death	8 (3.5)	11(3.8)	7 (5.4)
Graft Loss	15 (6.6)	11 (5.0)	10 (7.6)
Malignancy	5 (2.2)	10 (4.6)	4 (3.1)
Life-Threatening Adverse Event	2 (0.9)	3 (1.4)	4 (3.1)

1.FDA Analysis

The causes of death in study 302 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 26 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, acute tubular necrosis, and infected graft. There were no unusual or unexpected causes or rates for graft loss.

Nineteen patients developed biopsy-proven malignancy during the first twelve months post-transplant. Fifteen of the nineteen 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

colon and lung and several other types of cancer. No unusual or unexpected pattern of malignancy was detected.

Nine patients had other non-fatal life-threatening adverse events during the first twelve months post-transplant. Events included severe pneumonia due to infection with opportunistic organisms (*Aspergillus fumigatus*, CMV) and other complications which included cardiac arrest, respiratory arrest, pancreatitis and pulmonary embolism.

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.***

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 302, the rates of PTLD at 12 months were:

SRL 2	0.4%
SRL 5	2.3%
Placebo	0.0%.

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 significant. Despite the decreased use of anti-T-lymphocyte antibody in the SRL arms, the highest incidence of PTLD (2.3%) 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. A specific analysis of the CMV status of the kidney donor and kidney transplant recipient was performed for study 302. Of the 66 black patients in study 302, only 2(3%) were at "high risk" for CMV infection and disease i.e. they were CMV negative recipients of CMV positive donor kidneys.

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. However, regarding complications from cytomegalovirus infection—the African-American patients in study 302 appeared to be a low risk population to develop serious CMV infection and serious CMV disease.***

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 302.

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 302 except for a statistically significant higher incidence of mucosal *Herpes simplex (HSV)* in the sirolimus 5 mg group.

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. Either of these two antiviral drugs has 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.***

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 Study 302 .Data was not collected for HDL, LDL or apolipoproteins during Study 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 triglceride" 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 302 and thus no major bias should have affected these analyses.

TABLE 41 Study 302 Patients who developed hypercholesterolemia on study drug[1]

# study 302 patients	Placebo	Sirolimus 2 mg	Sirolimus 5 mg
Total # patients in each treatment arm	130	227	219
Patients. with pre-study chol.<200mg/dl	95/130 (73.1%)	163/227 (71.8%)	165/219 (75.3%)
Patients with normal baseline cholesterol who developed chol. ≥240 mg/dl on study drug	39/95 (41.1%)	123/163 (75.5%)	120/165 (72.7%)
Fisher's exact p-value		<0.0001	<0.0001

1. FDA analysis

Reviewer's note: ***A significant risk to develop new onset hypercholesterolemia , above and beyond the risk anticipated from cyclosporine, exists in the sirolimus treatment arms. The number of patients on sirolimus 2 mg (75.5%) and 5 mg (72.7%), who developed a new problem with elevated cholesterol, was significantly greater than the placebo control (41.1%).***

TABLE 42 Study 302 patients who developed hypertriglyceridemia on study drug[1]

Study 302 patients	Placebo	Sirolimus 2 mg	Sirolimus 5 mg
Total # patients in each treatment arm	130	227	219
Patients with pre-study TG≤200mg/dl	89/130 (68.5%)	168/227 (74.0%)	170 /219 (77.6%)
Patients with normal baseline TG who developed TG >500 mg/dl on study drug	2/89 (2.2)	26/168 (15.5)	40/170 (23.5)
Fisher's exact p-value		0.0006	<0.0001

1. FDA analysis

Reviewer's note: ***A significant risk to develop new-onset hypertriglyceridemia, above and beyond the risk anticipated from cyclosporine, exists in the sirolimus treatment arms. The number of patients on sirolimus 2 mg (15.5%) and 5 mg (23.5%), who developed a new problem with elevated cholesterol, was significantly greater than the placebo control (2.2%).***

Table 43 Analysis of the use of lipid lowering agents Study 302[1]

Study 302	Placebo	SRL 2 mg	SRL 5 mg
Patients with normal cholesterol pre-study	95	163	165
Patients initiated on lipid -lowering drug	15 (15.8%)	69 (42.3%)	77 (46.7%)
Patients who continued on lipid lowering drug at 6-12 months	11 (12%)	47 (29%)	64 (39%)

1. FDA analysis

Reviewer's note: ***In study 302, 15.8% of the placebo patients were initiated on lipid-lowering agents and 42.3% and 46.7% of the patients on sirolimus. Once initiated on a lipid-lowering agent, at least 60 % of these patients continued on the lipid lowering agent at study's end. The majority of the lipid- lowering agents used were HMG-CoA reductase inhibitors. Data concerning the number of patients initiated on lipid – lowering agents appeared to be complete.***

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.

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.

Table 44 Incidence of PTDM study 302

Study 302	SRL 2 (n= 152)	SRL 5 (n=150)	Placebo (n=84)
% patients who developed PTDM	2 (1.3)	4 (2.7)	0 (0)

APPEARS THIS WAY ON ORIGINAL

Reviewer's note: ***As depicted in Table 44, the incidence of PTDM was highest in the SRL 5 group, when compared to SRL 2 and placebo. However, the overall incidence of PTDM was small in study 302. PTDM occurred more commonly in the Black population and this is not unexpected. (see Table 45 below)***

Table 45 Incidence of PTDM in Study 302 by Race

Study 302 patients who developed PTDM by race	SRL 2 Black (n=11) Non-Black (n=141)	SRL 5 Black (n=17) Non-Black (n=133)	Placebo Black (n=7) Non-Black (n=77)
Black	1 (9.1)	2 (11.8)	0 (0)
Non-Black	1 (0.7)	2 (1.5)	0 (0)

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. 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 treatment groups in study 302. 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 post-hoc analyses using Nankivell GFR and serum creatinine were performed by both the Applicant and the FDA.***

In the following tables, one can see that in black and non-black patients the GFR was better in the group on Placebo 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. 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 had discontinued study drug. Thus, 11-14% of the study population was excluded from these exploratory analyses because of missing data. This could present a potential source of bias, particularly if availability of data at 12 months were related to the occurrence of an episode of rejection. However, it was determined that the population, included in these analyses remained

similar to the overall study population with respect to demographics and rates of acute rejection within each treatment group. The following tables present FDA's analyses.

Table 46 Study 302 GFR results at 12 months (337-393 days)[1]

Treatment	N observed /N total	Mean GFR (cc/min) +/- SD	p-value
Placebo	101/130 (77.7%)	61.7 +/- 18.18	-----
SRL 2 mg	190/227 (83.7%)	54.9 +/- 17.36	0.0022
SRL 5 mg	175/219 (79.9%)	52.9 +/- 18.29	0.001

1. FDA analysis

Table 47 Study 302 Creatinine at 12 months [1]

Treatment	N observed	Mean creatinine mg/dl +/- SD	p-value
placebo	102	1.96 +/- 1.77	
SRL 2	191	2.11 +/- 1.65	0.4295
SRL 5	180	2.11 +/- 1.32	0.4357

1. FDA analysis

Reviewer's note: The information available to date, suggests that sirolimus is not intrinsically nephrotoxic, but this data is limited. In particular, pre-clinical investigations to evaluate the effect of sirolimus on cyclosporine nephrotoxicity, have not been done (please see phase 4 commitments).

In the discussion of the evaluation of renal function post-transplant, it is important to note that study 302 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 Table 46 , the mean GFR at 12 months was lower in patients assigned to sirolimus compared to placebo. However, in Table 47, mean serum creatinine at 12 months was not significantly different across treatment groups. Note that the calculated GFR, that attempts to control for factors such as weight, height, gender and age, that may influence the interpretation of serum creatinine, displayed less variability than serum creatinine.

Episodes of acute rejection are expected to result in lower GFR. Therefore, it is also of interest to calculate mean GFR among those patients who did not experience a

rejection episode, to evaluate whether there was an underlying difference across treatment groups independent of rejection.

Early and late episodes of acute rejection may not have the same prognostic consequences on graft survival. Thus, because the mean time to acute rejection in SRL arms was later than in the placebo group, it became also of interest to compare, across treatment groups, GFR at 12 months among patients who had experienced at least one episode of acute rejection.

Table 48 Study 302 Mean GFR at 12 months (337-393 days)[1]

Treatment	N (obs)	Mean (SE) cc/min	p-value
Placebo			
Non-rejector	64	62.9 (2.29)	
Rejector	37	59.7 (2.96)	
SRL 2			
Non-rejector	147	57.29 (1.34)	.0329
Rejector	43	46.9 (2.84)	.0012
SRL 5			
Non-rejector	141	55.2 (1.46)	.0038
Rejector	34	43.5 (3.34)	.0001

1.FDA analysis

APPEARS THIS WAY ON ORIGINAL

Table 49 Study 302 Mean Serum Creatinine at 12 months (337-393 days)[1]

Treatment	N (obs)	Mean (SE) mg/dl	p-value
Placebo			
Non-rejector	65	1.84 (0.20)	
Rejector	37	2.17 (0.33)	
SRL 2			
Non-rejector	148	1.90 (0.10)	0.7923
Rejector	43	2.83 (0.38)	0.0527
SRL 5			
Non-rejector	145	1.96 (0.09)	0.5943
Rejector	35	2.72 (0.30)	0.1240

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 placebo. 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 placebo.***

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

There were 43 cases of HUS/TTP in studies 301 and 302.
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 in study 301 and 302, and only 3 patients lost their grafts(SRL 5 =2, SRL 2 = 1).

Table 50 Rate (%) of HUS/TTP at >12 months

Study 302	SRL 2 n=218	SRL 5 n=208	Placebo n=130
Percent patients with HUS/TTP	4(2.7%)	17 (8.2%)*	4 (3.2%)
p-value*	<0.05 SRL 5 vs SRL 2		

Table 51 Overall Rate (%) of HUS/TTP at >12 months

study	SRL 2 mg n=281 study 301 n=218 study 302	SRL 5 mg n=269 study 301 n=208 study 302	Placebo n=130	AZA n=161
301	5 (1.4%)	7 (2.6%)	-----	**3 (1.9%)**
302	4 (2.7 %)	**17 (8.2%)***	4(3.2%)3.2	-------
p-value*	<0.05 SRL 5 vs SRL 2			

***Reviewer's note:** There was a significantly increased number of HUS/TTP cases occurring in study 302 patients on SRL 5 mg. These cases were mainly clustered at one study site. No reason for this occurrence has been identified to date.*

Hematologic

APPEARS THIS WAY
ON ORIGINAL

Important points:

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 placebo. The applicant states that there were no platelet counts under 50 x 10^9/L after month 3.
Severe thrombocytopenia (<50 x 10^9/L) was rare (0.2%) and although epistaxis is reported in this trial there was only one episode of epistaxis associated with thrombocytopenia(<100x 10^9/L).

2)Leukopenia was significantly more frequent with sirolimus at 5 mg compared to sirolimus at 2 mg per day and placebo. 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 1x 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.***

Conclusions Regarding Efficacy Data include:

1) The results of both Phase III studies 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 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 placebo. The maximum difference that can be excluded with 97.5% certainty is acceptable.
3) It has not been adequately shown that the use of Rapamune® 5 mg/day, rather than Rapamune® 2 mg/day, for patients considered being at high risk for rejection significantly improves the rate of efficacy failure.

Conclusions Regarding Safety Data include:

1) Hyperlipidemia, thrombocytopenia and decreased GFR at one year continued to be significant problems for patients taking sirolimus in study 302.
2) When compared to the placebo 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: epistaxis, hypercholesterolemia, hyperlipemia (elevated triglycerides), increased LDH, tachycardia, and thrombocytopenia.
3) 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: anemia, chills, dysuria, ecchymosis, facial edema, fever, hyperlipemia (elevated triglycerides), hypokalemia, increased LDH, rash, thrombocytopenia, and TTP/HUS.
4) No major new safety issues surfaced in study 302 when compared to study 301.

8.1.2.5 Overall, Rapamune® 2 mg/day and 5mg/day are relatively safe.

9. Overview of Efficacy-Comparative results between studies.

This application was submitted to support the efficacy of sirolimus in a cyclosporine - based immunosuppressive regimen in the prevention of acute rejection in the allogeneic renal transplant recipient. The submission contained two large multi-center, randomized, double-blind, active and placebo controlled trials, conducted in the U.S. (study 301) and

in the U.S., Canada, Australia and Europe (study 302). Both pivotal studies 301 and 302 support the efficacy of sirolimus for the requested indication in renal transplantation. Patient and graft survival at 12 months were comparable to that seen in the control groups.

Neither study included patients at high risk for rejection such as re-transplants, multi-organ transplants, patients with high PRA or patients who required anti-lymphocyte induction therapy and consequently, no recommendations will be allowed in the label regarding the use of sirolimus in these populations. Additional study is required to ascertain if sirolimus will be efficacious in preventing acute rejection in these high risk groups.

The black population is also considered to be at higher risk for acute rejection. The results of study 301, which stratified for race, demonstrated that the black population had better efficacy with the azathioprine control (but not significantly better) when compared to sirolimus 2 mg/day. Black patients on the higher (5 mg/day) dose of sirolimus, had better efficacy (but not significantly better) when compared with sirolimus 2 mg/day and the azathioprine control. Therefore, if the transplant physician is considering whether to use the higher (5 mg dose) of Rapamune® in a black patient, it will be important for the physician to weigh any potential benefit against the risk of developing an adverse event such as hyperlipidemia. The Applicant recommends the use of the 5 mg/day sirolimus dose in high risk black transplant recipients and states that the black population had less adverse events than the non-black population in studies 301 and 302. However, the overall number of black patients who were maintained on sirolimus in these two pivotal trials was only 177 black patients. This is too small a safety database from which to draw definitive conclusions regarding adverse events that may occur with lower frequency. Additional studies on transplant recipients, at high risk for rejection, have been recommended as Phase 4 commitments.

10. Overview of Safety

10.1 Significant/Potentially Significant Events

Please see the safety sections of this review for a full discussion of the issues of sirolimus- associated: hyperlipidemia, renal function parameters (decreased GFR and increased serum creatinine at 12 months post-transplant), leukopenia, and thrombocytopenia, TTP/ hemolytic uremia syndrome(HUS), PTDM, infection and malignancy.

It is important to emphasize again that the incidence of certain adverse events with sirolimus were dose-dependent.

It is important to note that a significant number of patients who began the pivotal studies had no evidence of hyperlipidemia and, on sirolimus therapy, they developed a new problem which often required intervention with a lipid-lowering agent.

A significant number of patients on sirolimus in both studies 301 and 302 had elevated GFR when compared with the control groups. Both the reasons for this finding and its prognostic ramifications regarding graft survival remain to be determined.

Mean GFR was decreased among patients in the sirolimus treatment groups compared to controls in both studies 301 and 302. This was contrary to what would be expected based on differences in rates of acute rejection. It is believed that the occurrence of acute rejection is associated with decreased renal function at one year. Although the differences in mean GFR at one year between treatment groups was in the opposite direction predicted by differences in rates of acute rejection, within each treatment group the lowest mean GFR at 12 months was observed among those who had experienced at least one episode of acute rejection.

There are some limitations to the FDA's analysis, since data on serum creatinine at 12 months was missing for 11% to 14% of each group. However, these findings were consistent across two studies. Furthermore, mean GFR at 12 months was lowest for the SRL 5mg/day treatment group in both studies, which would be consistent with a dose-related effect.

The reasons for the differences in GFR at 12 months are uncertain. Although mean cyclosporine trough concentrations remained high, at or above the upper limit of the targeted range, throughout 12 months in both double blind studies, this was consistent across treatment groups.

Pre-clinical data to date does not suggest that sirolimus is intrinsically nephrotoxic. However, the potential for sirolimus to enhance cyclosporine nephrotoxicity has not been adequately evaluated, and should be the subject of phase IV pre-clinical investigations.

It is believed that the occurrence of acute rejection is associated with decreased renal function at one year. Although the differences in mean GFR at one year between treatment groups was in the opposite direction predicted by differences in rates of acute rejection, within each treatment group the lowest mean GFR at 12 months was observed among those who had experienced at least one episode of acute rejection.

Mean time to rejection was later in the sirolimus treatment groups compared to the control groups. Therefore, a difference in the impact of late versus early rejection on GFR should be considered. The monitoring schedule for serum creatinine is based, in part, on the expectation that the majority of episodes of acute rejection occur early post-transplantation, and is more frequent during the first few months. Thus, there exists a potential for delay in detection of later rejection episodes, compared to earlier episodes.

Decreases in mean GFR at one year, of the magnitude observed in these two studies, may predict a shorter time to kidney graft loss or failure, and a shorter graft half-life. Long term follow-up will be needed to evaluate whether graft survival remains similar over time among patients assigned to regimens of sirolimus plus cyclosporine and steroids compared to patients assigned to cyclosporine, steroids and azathioprine or placebo control.

10.1.1 Deaths

Deaths were rare in the first 12 months post transplantation, and were not increased in the sirolimus arms and no particular pattern was identified in either study.

10.1.2 Other Significant/Potentially Significant Events

Malignancies and PTLD did not occur at greater frequency in the sirolimus-treated patients during the first 12 months post transplantation. However, long-term follow-up will be necessary in order to obtain a more accurate assessment of the risks to develop malignancy that may be associated with long-term immunosuppression utilizing sirolimus.

10.1.3 Overdosage exposure

There is minimal experience with overdose. During clinical trials, there were two accidental Rapamune® ingestions of 120 mg and 150 mg. One patient, receiving 150 mg, experienced an episode of transient atrial fibrillation. The other patient experienced no adverse effects. General supportive measures should be followed in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte binding of Rapamune®, it is anticipated that Rapamune® is not dialyzable to any significant extent.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

Please see the individual study 301 and study 302 safety sections of this review for the adverse event incidence tables.

Change from baseline was used for the following laboratory parameters:
platelet count, creatinine phosphokinase, AST, LDH, cholesterol triglyceride, and potassium. Actual laboratory values were used for the following laboratory parameters:
serum creatinine and Nankivell GFR.

10.2.2 Laboratory Findings

Please refer to the safety sections of this review which discuss the main laboratory abnormalities identified in patients who were treated with sirolimus i.e. hyperlipidemia, anemia, thrombocytopenia, leukopenia, elevated serum creatinine.

10.2.3 Drug-Demographic Interactions

Analyses of drug-demographic interactions were presented by the Applicant in the Integrated Summary of Safety (Volume No. 330, dated December 15, 1998) and in the 3 Month Safety Update (dated March 15, 1999).

10.2.3.1 Age

The effect of age on the safety profile of sirolimus was examined by comparing groups of patients less than 18 years of age (n=11), 18 to 40 years of age (n=431), 41 to 65 years of age (n=763), and older than 65 years of age (n=65), combining patients from Study 301 and Study 302.

The incidence of treatment-emergent adverse events (TEAEs), as a function of age, was examined across these four groups. There were no notable differences between the group aged from 18 to 40 years and the group aged 41 to 65 years. Asthenia, dyspnea, and anemia were more frequently reported in the group aged greater than 65 years.

No notable differences were demonstrated between age groups with respect to laboratory abnormalities.

Because of the small number of subjects less than 18 years or greater than 65 years, it is not possible to determine whether these groups would respond differently than patients aged 18 to 65.

10.2.3.2 Gender

The effect of gender on safety and tolerance was examined by comparing data from 659 men and 318 women treated with sirolimus in studies 301 and 302 combined. No notable differences in TEAEs were detected between men and women with the exception of a greater incidence of urinary tract infections among women compared to men. No notable differences in the occurrence of laboratory abnormalities were detected between men and women. In particular, no notable differences were found between men and women with respect to the incidence of clinically important abnormalities associated with immunosuppression and the use of sirolimus, identified in studies 301 and 302.

10.2.3.3 Ethnic Origin

As noted in the individual phase 3 studies, the black population did not demonstrate a significant decrease in efficacy failure with either dose of sirolimus, compared to placebo or azathioprine controls.

The effect of ethnic origin was examined by comparing data from 223 Black, 114 Hispanic and 923 "other" patients from Studies 301 and 302 combined. The patient population labeled "other" included predominantly white patients plus Asian and other miscellaneous populations.

Hyperlipemia (elevated triglycerides) was more frequently reported in the "other" (31%) and hispanic (47%) groups than in the Black patients (24%). The frequency of hyperglycemia (24%) was greater in Black patients than in the "other" group. Indeed, while the overall rate of post-transplant diabetes was low in both studies 301 and 302, it occurred more frequently in the Black population.

10.3. Human Reproduction Data

There is no data for the use of sirolimus in pregnancy, however the Applicant will create a pregnancy registry.

11. Labeling Review

The proposed Package Insert, included in the original NDA submission, was substantially revised after discussion between the FDA and the sponsor. The revision dated September 14, 1999 is the final version agreed upon, and it incorporates all of the successive changes requested by the FDA. Important changes included: The recommendation to use the 5 mg/day dosage of Rapamune® in "high risk" renal transplant recipients was not allowed. Any reference to the possibility of a synergistic interaction between Rapamune® and other immunosuppressants was not allowed. Adequate precautions and warnings were made regarding the adverse effects of hyperlipidemia and the findings of elevated serum creatinine and decreased GFR noted in patients receiving sirolimus, as compared to patients in the placebo and azathioprine control arms. Tabulations of the adverse reactions were broken down by study, instead of pooling events by treatment arm. This is necessary because of the differences between the study populations, and the stratification/randomization strategies use in study 301 ("study 1" in the label) and in study 302 ("study 2" in the label).

12. Conclusions

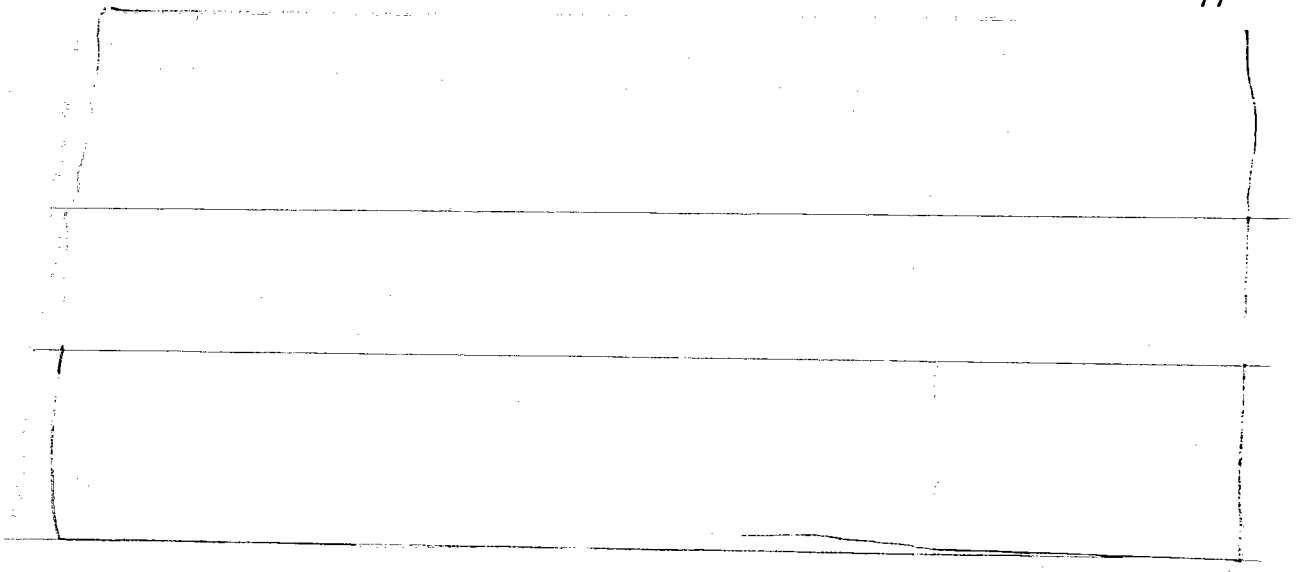
The Applicant has demonstrated that Rapamune® and cyclosporine-based therapy is comparable to cyclosporine-based therapy with and without azathioprine in preventing allograft rejection in renal transplant recipients. Important aspects of the safety profile of Rapamune® in renal transplant recipients include adverse events such as hyperlipidemia, decreased GFR at one year post-transplant, leukopenia and thrombocytopenia. A better understanding of the human pharmacokinetics and pharmacodynamics of sirolimus may improve its safety margin. Further exploration regarding the etiology of the decreased twelve month GFR, for patients treated with sirolimus, is warranted.

The risks associated with the use of sirolimus in renal transplantation must be weighed against the consequences of uncontrolled allograft rejection. Overall, there is a reasonable balance between the risks and benefits of sirolimus-based immunosuppressive therapy when used for the prophylaxis of organ rejection in patients receiving cadaveric, living-related and living-unrelated renal transplants. Both the 2mg/day and 5 mg/day doses of Rapamune® are safe and effective. However, no efficacy benefit was conferred using the higher dose of Rapamune® and, in fact, an increase in the frequency of certain adverse events such as hyperlipidemia and hematologic events was noted. Long-term follow-up will be essential in order to better ascertain the long-term cardiovascular and cerebrovascular consequences of the hyperlipidemia associated with Rapamune® .

13. Recommendations

13.1 Approval

The 2 mg/day and 5 mg/day doses of Rapamune® should be approved for the prophylaxis of organ rejection in renal transplant recipients. Although a daily maintenance dose of 5 mg , with a loading dose of 15 mg, was used in clinical trials and was shown to be safe and effective, no efficacy advantage over the 2 mg dose could be established for renal transplant patients.



Recommended:

1) Nephrotoxicity studies with combinations of Rapamune® and cyclosporine as well as other immunosuppressants (e.g. FK506 and MMF).
2) Evaluation of the effect of sirolimus on long term renal function as measured by glomerular filtration rate (GFR) in patients receiving kidney or other solid organ transplants.
3) Evaluation of the impact of sirolimus on liver function tests in recipients of kidney or liver transplants who may have hepatitis B and or hepatitis C virus infection.
4) Studies to evaluate the interaction of Rapamune® with calcium channel blockers including at least one drug in each class of the currently marketed agents.

14. Pertinent Advisory Committee Minutes

On July 27, 1999 the Antiviral Drugs Advisory Subcommittee on Immunosuppressant Drugs met to discuss the safety and efficacy data for sirolimus (NDA 21-083). The following questions were posed to the eleven voting members and three non-voting guests on the committee.

1. Is sirolimus safe and effective for the prevention of acute rejection in patients receiving allogeneic renal transplants? Votes: Yes =11, No = 0

The subcommittee agreed that sirolimus was safe and effective for the prevention of acute rejection in patients receiving allogeneic renal transplants at a recommended dose of 2 mg/day.

2. Is there a need for an alternate dose in specific populations?

The subcommittee agreed that an alternate dose might be needed for specific populations. However, the information presented in studies 301 and 302 did not support the sponsor's recommendation of a 5 mg/day dose for patients at high risk

for rejection. However, the majority of the subcommittee did recommend the inclusion of the 5 mg data in the package insert.

3. What additional phase IV studies would you recommend?

The subcommittee recommendations for phase IV studies included studies of:

The remaining questions from the Agency were answered by discussion, and not by a formal vote. Please see the summary minutes dated July 27, 1999.

/S/

Rosemary Tiernan, M.D. 9/22/99
Medical Officer HFD-590

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival IND [redacted] /NDA 21-083

HFD-590/Division File
HFD-104/ODEIV-Dir/Kweder
HFD-590/DivDir/Goldberger
HFD-590/DepDivDir/Albrecht
HFD-590/CPMS/Frank
HFD-590/RPM/Bacho
HFD590/MOTL/Cavaillé-Coll
HFD-590/MO/Tiernan
HFD-590/Chem-TL/Schmuff
HFD-590/Chem/Seggel
HFD-590/PharmTox-TL/Hastings
HFD-590/PharmTox/Kunder
HFD-590/Micro-TL/Lard
HFD-590/Micro/Bala
HFD-725/Stat-TL/Silliman
HFD-725/Stat/Dixon
HFD-880/Biopharm-TL/Ajayi
HFD-880/Biopharm/Kumi
HFD-104/ADRA/Hassall
HFD-104/Kweder
HFD-600/Office of Generic Drugs
HFD-104/Murphy
HFD-340

Concurrence

HFD-590/DivDir/Goldberger /S/ 9/22/99
HFD-590/ MO-TL/Cavaillé-Coll

/S/ 9.22.99

APPEARS THIS WAY
ON ORIGINAL

DFS Keywords

Class immunosuppressant, other
Indic transplant, kidney