

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021083

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

AUG 20 1999

NDA #: 21-083

Applicant: Wyeth-Ayerst Laboratories

Name of Drug: Rapamune® (Sirolimus) Oral Solution

Documents Reviewed: Reissued NDA Index and Summary sections (Vol. 2.1 and 2.2) dated January 6, 1999, Statistical sections (Vols. 1.332-1.362) dated December 15, 1998, revised ISE dated June 1, 1999, revised efficacy SAS datasets dated May 17, 1999, and the electronic regulatory review aid on the Wyeth-Ayerst server which contained the NDA paper volumes, the CRF's and CRT's, and SAS datasets of the clinical data.

Indication: Prophylaxis of organ rejection in patients receiving renal transplants.

Statistical Reviewer: Cheryl Dixon, Ph.D.

Medical Reviewer: Dr. Rosemary Tiernan (HFD-590)

I. Introduction

Rapamune® Oral Solution is an immunosuppressive agent for the prophylaxis of organ rejection in patients receiving renal transplants. Acute allograft rejection occurring within the first 6 months following transplantation is a significant clinical problem. Early acute rejection episodes (those diagnosed within the first 6 months after transplantation), especially those of severe grade or with permanent functional deterioration, are frequently associated with a higher incidence and an earlier onset of chronic rejection and shortened graft longevity.

The clinical program for the study of Rapamune® consisted of 50 studies in which more than 2800 patients and volunteers were enrolled. Two large, adequate and well-controlled, randomized, double-blind, phase III studies in primary mismatched renal allograft recipients were performed to demonstrate the safety and effectiveness of Rapamune® in preventing the occurrence of the first biopsy-confirmed acute rejection during the first 6 months after transplantation, without adversely affecting patient and graft survival. In both studies, all patients received a protocol-defined regimen of cyclosporine (CsA) and corticosteroids.

Study 301, conducted in the United States, was a double-blind, controlled trial with azathioprine as a comparator. Study 302, conducted in Australia, Europe, and North America, was a double-blind placebo controlled trial. Both comparative regimens (CsA/corticosteroids and CsA/corticosteroids/azathioprine) are well-established regimens for recipients of primary renal allografts. One thousand two hundred ninety-five patients were enrolled in the two studies: 719 in study 301 and 576 in study 302.

In addition to the comparator arm, each study consisted of two fixed dose Rapamune[®] treatment groups (2 mg/day and 5 mg/day). Patients were randomly assigned to one of three treatment groups in a 2:2:1.1 ratio to receive CsA/corticosteroids plus either Rapamune[®] 2 mg/day or 5 mg/day or matching comparator. This randomization ratio was chosen to maximize the number of patients exposed to Rapamune[®] and to minimize the potential influence of incomplete data from patients in the control groups. The time of randomization differed between studies. In study 301, patients were randomized to treatment group within 24 to 48 hours after transplantation. In study 302, patients were randomized immediately before transplantation. Randomization after transplantation allowed investigators in study 301 to enroll a population with fewer perioperative complications.

Each study was stratified by two variables. Both studies were stratified by center. Due to an increased risk for acute rejection and graft loss experienced by black transplant recipients, ethnic origin is a variable of interest. Study 301 was expected to enroll a greater proportion of black patients than study 302. Therefore, stratification by ethnic origin (black or nonblack) within center was chosen for study 301. The other variable of interest was donor origin (cadaver vs. living). Therefore, stratification by donor origin within center was chosen for study 302.

As stated in the protocols, the primary endpoint in both studies was efficacy failure in the first 6 months (194 days) after transplantation. Efficacy failure was defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death. Prospectively defined secondary endpoints were patient and graft survival 1 year after transplantation, the use of antibody therapy to treat the first episode of biopsy-confirmed acute rejection, incidence of acute rejection, histological grade of the first biopsy-confirmed acute rejection, and incidence of treatment failure. Treatment failure was defined as the first occurrence of biopsy-confirmed acute rejection or premature discontinuation from study medication for any reason within the first 6 months after transplantation.

Reviewer's Note: The Division considers efficacy failure at 6 months and patient and graft survival at 1 year co-primary endpoints. This is to ensure that patient and/or graft survival is not adversely affected by reducing early acute rejections.

For the purpose of determining sample size, efficacy failure rates at 6 months were estimated to be 18% for the Rapamune[®] treatment groups, 36% for the azathioprine control group, and 40% for the placebo control group. After adjusting for a 2:2:1.1

randomization, the sample sizes for the two studies were as follows. For study 301, 234 patients were needed in each of the two Rapamune[®] treatment groups and 132 patients were needed in the azathioprine control group in order to have 90% power to declare a significant difference in each comparison. For study 302, 164 patients were needed in each of the two Rapamune[®] treatment groups and 92 patients were needed in the placebo control group in order to have 90% power to declare a significant difference in each comparison. Each study enrolled beyond the minimum number stated in the protocol in order to ensure that the data from approximately 500 patients at or above, the recommended Rapamune[®] dose level would be available for safety analysis.

APPEARS THIS WAY
ON ORIGINAL

II. Efficacy Evaluation

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-Haenszel (CMH) statistic stratified by investigator. All patients assigned to treatment were included in this analysis. 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. The Breslow-Day statistic was used to test homogeneity of the treatment effect across strata. Patients defined as lost to follow-up were scored as efficacy failures, regardless of treatment assignment.

Since enrollment varied among centers, the data of centers with noninformative tables to the CMH statistic were pooled and analyzed as though they were from a single center. A center was defined as noninformative if all of the patients enrolled by a single investigator had the same outcome or if enrollment at a single center was so sparse that no patients were assigned to one of the treatments in the analysis. If the resulting center was still noninformative, then the smallest informative center was included in the pooled center.

Similarity with respect to patient and graft survival incidence rates was assessed with confidence intervals about the difference in rates (test drug - control). The lower bound of the confidence interval is used to assess the maximum decrease in patient and graft survival that one can safely exclude. These rates need to be taken into consideration when assessing the overall efficacy and safety of Rapamune[®].

Secondary endpoints defined as binary events and summarized by incidence rates were analyzed using Fisher's exact test. Survival and other time-to-event variables were analyzed by the log-rank test.

Reviewer's Note: On April 14, 1999, Wyeth-Ayerst notified the Division of a programming error in the SAS program that was used to create the efficacy analysis

datasets. This error caused an under-reporting of biopsy-confirmed rejections. When the efficacy analysis datasets were created, the acute rejections for investigators with alphanumeric identification numbers were not included. Upon further inspection, by this reviewer, of the raw data listings of the biopsy findings, several other biopsy-proven rejections were noted. These rejections were not included in the original analysis because the biopsy was not performed within the protocol stated two days of start of treatment for presumed rejection. It was agreed at a May 7, 1999 meeting with Wyeth-Ayerst that these events should be included in the analyses of acute rejection. In addition, from the time the original blinded database was frozen, there were a number of changes to the efficacy outcome designations for a number of patients due to on-going data clarification. Therefore, the analyses performed in this review are based on datasets that were received on May 17, 1999. These datasets were created from a more extensive updated database and used the expanded treatment window for acute rejection. This analysis is denoted as the inclusive analysis in the revised ISE submitted on June 1, 1999.

Study 301

- Patient Demographics

Study 301 was conducted at 40 centers in the United States: 38 centers enrolled patients. A total of 719 patients were enrolled in the study and randomized to one of the three treatment groups: 2 mg/day Rapamune® (n=284), 5 mg/day Rapamune® (n=274), and azathioprine (n=161). Nine patients were randomized into the study but did not receive at least one dose of study medication (3-Rapamune® 2 mg/day, 5-Rapamune® 5 mg/day, and 1-azathioprine). Reasons for discontinuation and not receiving study medication were noncompliance, protocol violation, patient treated with antibody, and myocardial infarction during surgery.

Table 1 shows demographic and baseline characteristics for all randomized patients. There were no statistically significant differences across treatment groups with the exception of gender. A significantly ($p < 0.001$) higher proportion of females were assigned to azathioprine (44%) than to either of the Rapamune® groups (27% 2 mg/day, 38% 5 mg/day). 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.

APPEARS THIS WAY
ON ORIGINAL

Table 1
Patient Demographics

	Rapamune® 2 mg/day	Rapamune® 5 mg/day	Azathioprine	P-value
# Patients	284	274	161	-
Gender N (%)				0.001
Female	76 (26.8)	103 (37.6)	71 (44.1)	
Male	208 (73.2)	171 (62.4)	90 (55.9)	
Age mean (SD)	44.9 (13.6)	46.9 (13.0)	45.4 (13.0)	0.173
Min, max	16, 79	13, 76	12, 69	
Race N (%)				0.935
Caucasian	160 (56.3)	154 (56.2)	92 (57.1)	
Black	63 (22.2)	61 (22.3)	42 (26.1)	
Hispanic	48 (16.9)	43 (15.7)	14 (8.7)	
Oriental (Asian)	7 (2.5)	10 (3.6)	10 (6.2)	
Other	6 (2.1)	6 (2.2)	3 (1.9)	
Donor Source N (%)				0.054
Cadaver	180 (63.4)	167 (60.9)	119 (73.9)	
Living (Related)	86 (30.3)	83 (30.3)	33 (20.5)	
Living (Unrelated)	18 (6.3)	24 (8.8)	9 (5.6)	

- **Analysis Results**

Table 2 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 (noninformative 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 azathioprine, 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 azathioprine.
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 azathioprine group.
5. The p-value of the Breslow-Day statistic used to test homogeneity of the treatment effect across strata.

The overall rates of efficacy failure in both Rapamune® treatment groups were significantly lower than the overall rate of efficacy failure in the azathioprine 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 treated with azathioprine. There was no significant difference in results across investigator sites, as shown by the Breslow-Day p-values.

Table 2
Efficacy Failure at 6 months

	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)	
Breslow-Day p-value	0.290	0.310	

Reviewer's Note: 97.5% confidence intervals are reported in the above table and all tables to follow. The 97.5% confidence intervals were calculated because of the Bonferroni correction applied to maintain an overall experiment-wise error rate of 0.05.

The incidence rates of efficacy failure at 6 months stratified by recipient race (black, non-black) are summarized in Table 3. There is a significant treatment effect for both Rapamune® treatment groups. This effect is not consistent across strata in the Rapamune® 2 mg/day treatment group (Breslow-Day $p=0.024$). The rate of efficacy failure is slightly higher in black patients treated with Rapamune® 2 mg/day than in black patients treated with azathioprine. For non-black patients, the rate of efficacy failure for the Rapamune® 2 mg/day group is lower than the rate for the azathioprine group. Efficacy failure rates are also lower for black and non-black patients in the Rapamune® 5 mg/day group as compared to azathioprine. When analyzing the subgroup of black patients only, however, the treatment effect seen for the Rapamune® 5 mg/day group is not statistically significantly different from azathioprine (Fisher's exact $p=0.102$). It should be noted, however, that the study was not powered to detect a significant treatment difference in the different subgroups.

Table 3
Efficacy Failure at 6 months Stratified by Recipient Race

	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 (32.2)
Blacks	22/63 (34.9)	11/61 (18.0)	14/42 (33.3)
Non-blacks	31/221 (14.0)	35/213 (16.4)	38/119 (31.9)
CMH p-value	0.002	0.001	
Breslow-Day p-value	0.024	0.928	

Table 4 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 indicate equivalence at a delta around 5-7%. 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 4
Patient and Graft Survival at 12 months

	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 (97.5% CI)	0.85 (0.35, 2.07)	1.175 (0.51, 2.72)	
Differences in rates (97.5% CI)	0.9 (-4.8, 6.6)	-1.1 (-7.1, 4.9)	

Table 5 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. 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 indicate equivalence at a delta around 5-6%. 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.

APPEARS THIS WAY
ON ORIGINAL

Table 5
Patient Survival at 12 months

	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)	

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. There is a trend toward less severe rejections in both Rapamune® groups.

Table 6
Histological Grade of Acute Rejection at 6 Months

	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, -)
p-value	0.006, 1.0 ^c	0.025, 0.241	

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

Rates of efficacy failure were calculated for the following subgroups: 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 group 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 are relatively small.

APPEARS THIS WAY ON ORIGINAL	Table 7 Efficacy Failure at 6 months Selected subgroups		APPEARS THIS WAY ON ORIGINAL
Subgroup	Rapamune® 2 mg/day (n=284)	Rapamune® 5 mg/day (n=274)	Azathioprine (n=161)
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

APPEARS THIS WAY ON ORIGINAL

Female patients had numerically lower efficacy failure rates in both Rapamune® groups when compared to females in the azathioprine group. Male patients in both Rapamune® groups had significantly lower efficacy failure rates than male patients in the azathioprine group. Females treated with Rapamune® have similar or slightly higher efficacy failure rates than their male counterparts but females treated with azathioprine have lower efficacy failure rates than males treated with azathioprine.

Patients who received a cadaveric donor organ had significant improvement in efficacy failure rates with Rapamune® 5 mg/day when compared to azathioprine. Those patients treated with Rapamune® 2 mg/day only had numerically lower rates when compared to azathioprine. Patients in both Rapamune® groups who received a living donor organ had lower efficacy failure rates than patients who received a living donor organ treated with azathioprine. These differences were only significant in the patients who received a living related donor organ due to the small number of patients who received a living unrelated donor organ. The efficacy failure rate of approximately 43% for patients who received a living donor organ treated with azathioprine may be higher than expected.

Patients with 3 to 6 HLA mismatches have higher efficacy failure rates than patients with 0 to 2 HLA mismatches. Both doses of Rapamune® show significant improvement in efficacy failure when compared to azathioprine for patients with 3 to 6 HLA mismatches. 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 azathioprine group.

A post-hoc logistic regression was used to determine which explanatory variables, if any, could be a predictor of efficacy failure during the first 6 months. The model was

forced to include treatment (Rapamune® 2 mg/day, 5 mg/day, and azathioprine) as independent variables. The other explanatory variables which were tested in a stepwise fashion included: recipient race (black, non-black), donor source (cadaver, living), recipient gender (female, male), number of HLA mismatches (continuous), cold ischemia time, donor age, and recipient age. The results for the final logistic regression model are presented in Table 8.

Table 8
Final Logistic Regression Model for Efficacy Failure

Independent Variable	Parameter		Odds Ratio
	Estimate	p-value	
Intercept	-1.3307	0.0001	
Rapamune2	-0.7150	0.0019	0.489
Rapamune5	-0.8627	0.0003	0.422
Race	0.4252	0.0431	1.530
HLA Mismatches	0.1367	0.0213	1.146

APPEARS THIS WAY
ON ORIGINAL

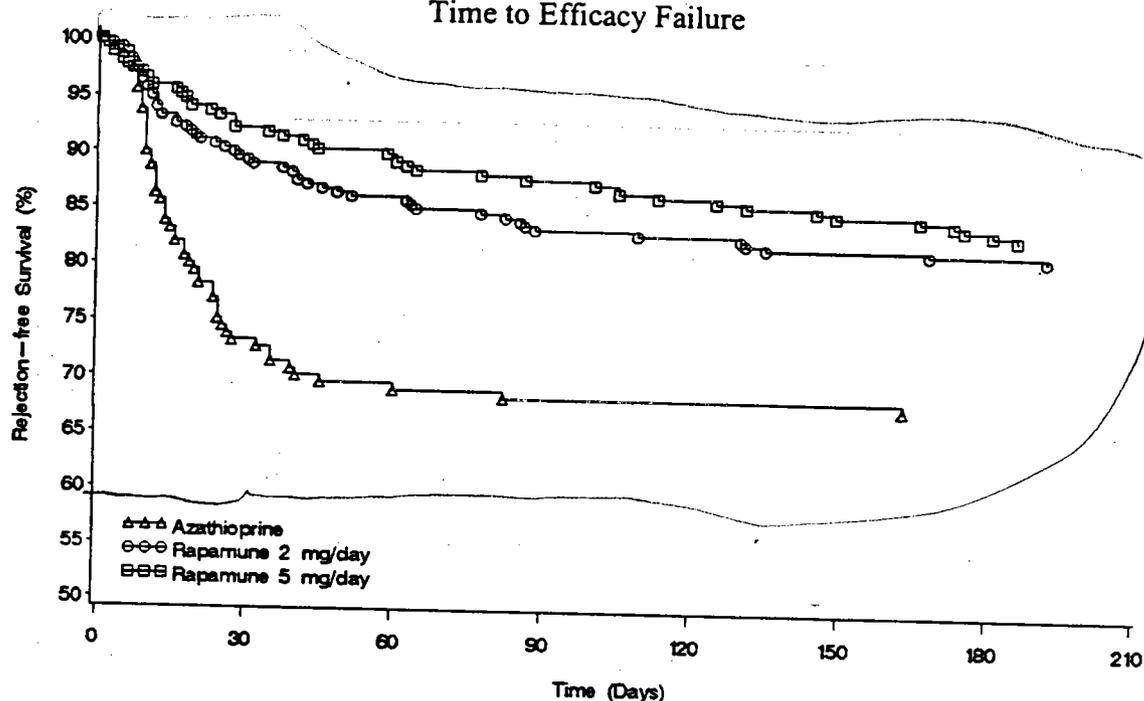
APPEARS THIS WAY
ON ORIGINAL

In addition to treatment effect, the final logistic model included the effect of recipient race and the number of HLA mismatches. The results of the final logistic regression model indicate that treatment with either dose of Rapamune® improves the odds against efficacy failure compared to treatment with azathioprine. The results also indicate that the odds of efficacy failure increase with increasing number of HLA mismatches and if the patient is black. These results support those presented in Table 3 and Table 7.

Figure 1 shows the time to efficacy failure in each treatment group during the first 6 months of treatment. The time to efficacy failure was significantly longer for the Rapamune® 2 mg/day group (log-rank, $p=0.0005$) and the Rapamune® 5 mg/day group (log-rank, $p < 0.0001$) than for the azathioprine group. The majority of the events occur within the first 30 to 60 days post transplantation and the majority of the event that occurred following 60 days occurred in the Rapamune® treatment groups.

APPEARS THIS WAY
ON ORIGINAL

Figure 1
Time to Efficacy Failure



A first biopsy-confirmed rejection episode occurred after 60 days from time to transplant in 27 patients: 13 patients in the Rapamune[®] 2 mg/day group, 13 in the Rapamune[®] 5 mg/day group, and 1 in the azathioprine group. One Rapamune[®] 2 mg/day rejection and 2 Rapamune[®] 5 mg/day rejections were Grade III (severe). Four Rapamune[®] 2 mg/day rejections and 3 Rapamune[®] 5 mg/day rejections were Grade II (moderate). The remaining rejections were Grade I (mild) including the 1 azathioprine rejection. All of these patients were alive with a functioning graft at 12 months.

The proposed labeling for Rapamune[®] is currently recommending that both doses be made available for clinical use. It is being proposed that the 2 mg/day dose be considered for use in the majority of patients, but that the 5 mg/day dose may provide an incremental benefit to patients at higher risk for acute rejection. Patients that could be considered at higher risk include patients who are: African American, those receiving second or third transplants, those with high panel reactive antibodies (PRA), and those with high degrees of HLA mismatch. This study was not designed to specifically enroll high-risk patients. Only patients receiving their first renal transplant were enrolled and patients who required antibody induction therapy were excluded. These patients may be considered as those at higher risk. In order to perform a meaningful subset analysis, the Medical Team Leader provided a definition of a high-risk group using factors stated in registry information that are recognized as having a predictive value on acute rejection. In this definition, a patient was considered to be at high-risk if they received a cadaveric donor organ and at least one of the following situations was satisfied: cold ischemia time was greater than 24 hours, PRA was greater than 50%, or there were more than 2 HLA mismatches.

Table 9 summarizes the results of the analysis of efficacy failure for the high-risk group as defined by the Medical Team Leader. There is a decrease in the incidence of efficacy failure rates for both Rapamune® doses when compared to azathioprine, but this difference is not statistically significant (Fisher's exact, $p=0.297$ Rapamune® 2 mg/day vs. azathioprine and $p=0.119$ Rapamune® 5 mg/day vs. azathioprine). The comparison of the two Rapamune® dose groups is not statistically significant either ($p=0.567$). For completeness, Table 9 also includes the results of the patients who were not considered at high-risk using the Medical Team Leader's definition. For this group of patients, both Rapamune® dose groups had significantly lower efficacy failure rates than the azathioprine group ($p=0.0006$ Rapamune® 2mg/day vs. azathioprine, $p=0.0006$ Rapamune® 5 mg/day vs. azathioprine). There was no significant difference between Rapamune® dose groups ($p=1.0$).

Table 9
Efficacy Failure at 6 months for patients considered at high-risk

	Rapamune® 2 mg/day (n=284)	Rapamune® 5 mg/day (n=274)	Azathioprine (n=161)
High-risk group	35/149 (23.5)	27/132 (20.5)	29/96 (30.2)
Non-high-risk group	18/135 (13.3)	19/142 (13.4)	23/65 (35.4)

There are some limitations with the above definition of a high-risk group. With this definition, at least half of the patients in each of the treatment groups are considered to be at high risk. In addition, the high-risk controls have lower efficacy failure rates than the non-high risk controls.

Study 302

- 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).

Table 10 shows 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.

Table 10
Patient Demographics

	Rapamune [®] 2 mg/day	Rapamune [®] 5 mg/day	Placebo	P-value
# Patients	227	219	130	-
Gender N (%)				0.588
Female	79 (34.8)	70 (32.0)	39 (30.0)	
Male	148 (65.2)	149 (68.0)	91 (70.0)	
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 (75.8)	175 (79.9)	103 (79.2)	
Black	26 (11.5)	27 (12.3)	13 (10.0)	
Asian	10 (4.4)	7 (3.2)	3 (2.3)	
Hispanic	6 (2.6)	2 (0.9)	4 (3.1)	
Australian aborigine	3 (1.3)	1 (0.5)	0	
Other	10 (4.4)	7 (3.2)	7 (5.4)	
Donor Source N (%)				0.407
Cadaver	173 (76.2)	174 (79.5)	99 (76.1)	
Living (Related)	39 (17.2)	29 (13.2)	27 (20.8)	
Living (Unrelated)	15 (6.6)	16 (7.3)	4 (3.1)	

- **Analysis Results**

Table 11 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 (noninformative 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.
5. The p-value of the Breslow-Day statistic used to test homogeneity of the treatment effect across strata.

The overall rates of efficacy failure in both Rapamune[®] treatment groups were significantly lower than the overall rate of efficacy failure 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 treated with placebo. There was no significant difference in results across investigator sites, as shown by the Breslow-Day p-values.

Table 11
Efficacy Failure at 6 months

	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)	
Breslow-Day p-value	0.169	0.377	

Table 12 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 significantly lower efficacy failure rates than patients receiving an allograft from a cadaver or living donor treated with placebo (Fisher's exact p=0.049 and 0.002, cadaver and living, respectively). The effect is not consistent across strata in the Rapamune® 5 mg/day treatment group (Breslow-Day p=0.029). 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 12
Efficacy Failure at 6 months Stratified by Donor Origin

	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 (43.4)
Living	14/54 (25.9)	8/45 (17.8)	19/31 (61.3)
CMH p-value	0.001	0.001	
Breslow-Day p-value	0.071	0.029	

Reviewer's Note: The results in Table 12 for the Rapamune® 2 mg/day are slightly different than those presented by the sponsor because one patient who received a living related donor organ was coded as a cadaver donor organ in their analysis.

Table 13 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 indicate equivalence at a delta around 5-6%. 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.

Table 13
Patient and Graft Survival at 12 months

	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 (97.5% CI)	0.82 (0.41, 1.64)	0.74 (0.37, 1.51)	
Differences in rates (97.5% CI)	2.2 (-6.3, 10.7)	3.2 (-5.2, 11.6)	

Table 14 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 indicate equivalence at a delta around 5%. 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.

Table 14
Patient Survival at 12 months

	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 (97.5% CI)	0.65 (0.21, 2.03)	0.93 (0.33, 2.68)	
Differences in rates (97.5% CI)	1.9 (-3.9, 7.7)	0.4 (-5.7, 6.5)	

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 placebo group. For patients who had an acute rejection, the distribution of histological grade of acute rejection is not different between treatment groups. There is a trend toward less severe rejections in both Rapamune® groups.

Table 15
Histological Grade of Acute Rejection at 6 Months

	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, -)
p-value	0.006, 0.335 ^c	0.001, 0.056	

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

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 group 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 are relatively small.

Table 16
Efficacy Failure at 6 months
Selected subgroups

Subgroup	Rapamune® 2 mg/day (n=227)	Rapamune® 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

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.

Reviewer's Note: Sixty of the 66 black patients enrolled in study 302 were from the centers in the United States. In the remaining 6 black patients, 5 were from centers in Canada and 1 from a center in Sweden.

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 failure rates than male patients in the placebo group. Females treated with Rapamune® have similar or slightly higher efficacy failure rates than their male counterparts but females treated with placebo have lower efficacy failure rates than males treated with placebo.

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 who received a living donor organ and were treated with placebo. 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 subgroupings could not be detected because of the small number of patients in these subgroupings.

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.

As described in the discussion of analysis results for study 301, a post-hoc logistic regression was used to determine which explanatory variables, if any, could be a predictor of efficacy failure during the first 6 months. Again, the model was forced to include treatment (Rapamune® 2 mg/day or 5 mg/day, placebo) as independent variables. The results for the final logistic regression model are presented in Table 17.

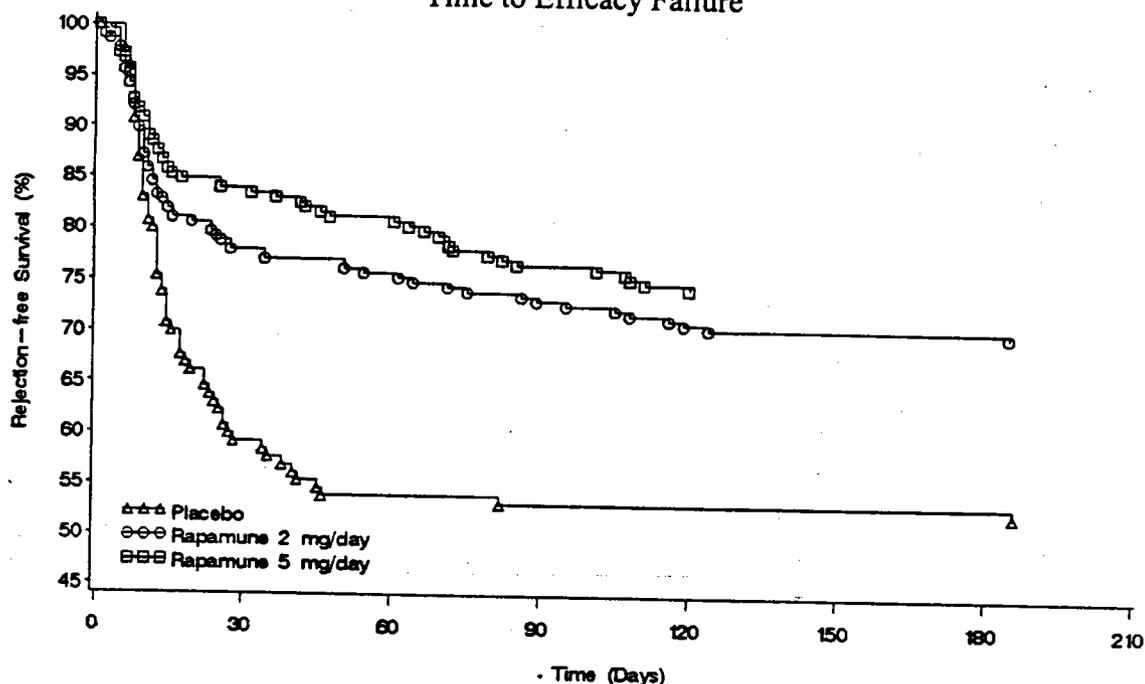
Table 17
Final Logistic Regression Model for Efficacy Failure

Independent Variable	Parameter Estimate	p-value	Odds Ratio
Intercept	-0.9389	0.0014	
Rapamune2	-0.8384	0.0003	0.432
Rapamune5	-0.9996	0.0001	0.368
HLA Mismatches	0.2466	0.0002	1.280

In addition to treatment effects, the final logistic model included the effect of the number of HLA mismatches. The results of the final logistic regression model indicate that treatment with either dose of Rapamune® improves the odds against efficacy failure compared to treatment with placebo. The results also indicate that the odds of efficacy failure increase with increasing number of HLA mismatches.

Figure 2 shows the time to efficacy failure in each treatment group during the first 6 months of treatment. The time to efficacy failure was significantly longer for the Rapamune® 2 mg/day group (log-rank, $p=0.0007$) and the Rapamune® 5 mg/day group (log-rank, $p < 0.0001$) than for the placebo group. The majority of the events occur within the first 30 to 60 days post transplantation and the majority of the event that occurred following 60 days occurred in the Rapamune® treatment groups.

Figure 2
Time to Efficacy Failure



A first biopsy-confirmed rejection episode occurred after 60 days from time to transplant in 24 patients: 12 patients in the Rapamune® 2 mg/day group, 10 in the Rapamune® 5 mg/day group, and 2 in the placebo group. Only one Rapamune® 5 mg/day rejection was Grade III (severe). Six Rapamune® 2 mg/day rejections, 2 Rapamune® 5 mg/day rejections, and both placebo rejections were Grade II (moderate). The remaining rejections were Grade I (mild). One Rapamune® 2 mg/day patient who had a mild rejection after 60 days died following the rejection but within 1 year post transplant. Three patients with a rejection after 60 days had a graft loss following the rejection that occurred within 1 year post transplant. These patients were one Rapamune® 2 mg/day patient who had a mild rejection, one Rapamune® 2 mg/day patient who had a moderate rejection, and one Rapamune® 5 mg/day patient who had a mild rejection.

Table 18 summarizes the results of the analysis of efficacy failure for the high-risk group as defined by the Medical Team Leader (see discussion in study 301 for definition). There is a statistically significant decrease in the incidence of efficacy failure rates for both Rapamune® doses when compared to placebo (Fisher's exact, $p=0.020$ Rapamune® 2 mg/day vs. placebo and $p=0.003$ Rapamune® 5 mg/day vs. placebo). The comparison of the two Rapamune® dose groups is not statistically significant ($p=0.517$). For completeness, Table 18 also includes the results of the patients who were not considered at high-risk using the Medical Team Leader's definition. For this group of patients, both Rapamune® dose groups had significantly lower efficacy failure rates than the placebo group ($p=0.025$ Rapamune® 2 mg/day vs. placebo, $p=0.004$ Rapamune® 5

mg/day vs. placebo). There was not a significant difference between Rapamune® dose groups ($p=0.581$).

Table 18
Efficacy Failure at 6 months for patients considered at high-risk

	Rapamune® 2 mg/day (n=227)	Rapamune® 5 mg/day (n=219)	Placebo (n=130)
High-risk group	47/142 (33.1)	39/134 (29.1)	38/76 (50.0)
Non-high-risk group	21/85 (24.7)	17/85 (20.0)	24/54 (44.4)

III. Safety Evaluation

The following is a review of the safety data for each Phase III study submitted by the sponsor. Even though the studies were similarly designed, a pooled safety analysis will not be presented. Since there are possible differences in the method of reporting adverse events in European studies and the organ pool in European countries is different from the organ pool in the United States, the safety results for study 302 will be presented separately from study 301.

The focus of this section will be treatment emergent adverse events (TEAEs) reported during the first 6 months of the study. TEAEs were adverse events not present at baseline or events present at baseline that worsened during treatment. In addition, analyses of the clinical laboratory parameters for renal function at 12 months will be presented. The laboratory parameters used to assess renal function are GFR (glomerular filtration rate) and serum creatinine. For a more complete review of the safety data including updated safety through 12 months, please refer to the Medical Officer's review.

Study 301

Of the 719 patients enrolled in the study, 709 received at least one dose of study medication and were valid for safety: 281 Rapamune® 2 mg/day patients, 269 Rapamune® 5 mg/day patients, and 159 azathioprine patients. One or more TEAEs that were not related to infection were reported during the on-treatment segment of the study by 279 (99%) Rapamune® 2 mg/day patients, 262 (97%) Rapamune® 5 mg/day patients, and 154 (97%) azathioprine patients. The most commonly occurring TEAEs during the on-therapy period (reported in at least 20% of patients in any one treatment group) and the accompanying p-values are summarized by treatment group in Table 19.

Table 19
Number (%) of Patients Reporting Treatment Emergent Adverse Events ($\geq 20\%$)

Body system Event	Rapamune [®] 2 mg/day (n=281)	Rapamune [®] 5 mg/day (n=269)	Azathioprine (n=159)	p-value
Any adverse experience (1 or more)	279 (99)	262 (97)	154 (97)	0.105
Body as a whole				
Abdominal pain	43 (15)	55 (20)	31 (19)	0.253
Asthenia	66 (23)	70 (26)	34 (21)	0.548
Pain	47 (17)	54 (20)	27 (17)	0.562
Cardiovascular system				
Hypertension	96 (34)	89 (33)	35 (22)	0.017*
Digestive system				
Constipation	68 (24)	78 (29)	53 (33)	0.110
Diarrhea	50 (18)	74 (28)	18 (11)	<0.001*
Nausea	66 (23)	69 (26)	47 (30)	0.381
Vomiting	40 (14)	39 (14)	36 (23)	0.053
Hemic and lymphatic system				
Anemia	56 (20)	73 (27)	32 (20)	0.096
Metabolic and nutritional				
Creatinine increased	61 (22)	64 (24)	32 (20)	0.669
Hypercholesteremia	84 (30)	94 (35)	34 (21)	0.012*
Hyperlipemia	83 (30)	103 (38)	29 (18)	<0.001*
Hypophosphatemia	45 (16)	56 (21)	28 (18)	0.337
Peripheral edema	137 (49)	134 (50)	68 (43)	0.343
Nervous system				
Tremor	60 (21)	64 (24)	25 (16)	0.136
Skin and appendages				
Acne	67 (24)	49 (18)	18 (11)	0.004*
Study event associated with miscellaneous factors				
Local reaction to procedure	106 (38)	106 (39)	53 (33)	0.453

*Overall difference among treatment groups assessed by Fisher's exact test.

Individual pairwise comparisons were performed for adverse events that were statistically significantly different among treatment groups. Significantly higher incidence rates in both Rapamune[®] doses compared to azathioprine were seen for hypertension and hyperlipemia. The rate of hyperlipemia was also significantly higher in the Rapamune[®] 5 mg/day group than in the Rapamune[®] 2 mg/day group. The rate of diarrhea was significantly higher in the Rapamune[®] 5 mg/day group than either the Rapamune[®] 2 mg/day group or the azathioprine group. The rate of hypercholesteremia was significantly higher in the Rapamune[®] 5 mg/day group than in the azathioprine group. Acne had significantly higher incidence rates in the Rapamune[®] 2 mg/day group than in the azathioprine group.

Table 20 lists the frequency of clinically important TEAE by treatment group. TEAE were identified as clinically important based on incidence rates, the relevance to the renal transplantation population, and/or safety data from previous Rapamune[®] trials.

Table 20
 Number (%) of Patients Reporting Clinically Important TEAE
 Excluding Infection and Malignancy

Body system Event	Rapamune® 2 mg/day (n=281)	Rapamune® 5 mg/day (n=269)	Azathioprine (n=159)	p-value
Body as a whole				
Headache	44 (16)	50 (19)	12 (8)	0.005*
Lymphocele	33 (12)	36 (13)	4 (3)	<0.001*
Cardiovascular system				
Hypertension	96 (34)	89 (33)	35 (22)	0.017*
Digestive system				
Diarrhea	50 (18)	74 (28)	18 (11)	<0.001*
Liver function tests abnormal	24 (9)	26 (10)	14 (9)	0.381
Endocrine system				
Diabetes mellitus	14 (5)	22 (8)	8(5)	0.256
Hemic and lymphatic system				
Anemia	56 (20)	73 (27)	32 (20)	0.096
Leukopenia	14 (5)	28 (10)	17 (11)	0.027*
Thrombocytopenia	25 (9)	47 (17)	9 (6)	<0.001*
Thrombotic thrombocytopenia purpura (TTP)	2 (<1)	4 (1)	0	0.283
Metabolic and nutritional				
Creatinine increased	61 (22)	64 (24)	32 (20)	0.669
Healing abnormal	22 (8)	24 (9)	6 (4)	0.120
Hypercholesteremia	84 (30)	94 (35)	34 (21)	0.012*
Hyperglycemia	34 (12)	39 (14)	18 (11)	0.581
Hyperkalemia	34 (12)	22 (8)	30(19)	0.005*
Hyperlipemia	83 (30)	103 (38)	29 (18)	<0.001*
Peripheral edema	137 (49)	134 (50)	68 (43)	0.343
Musculoskeletal system				
Arthralgia	40 (14)	53 (20)	18 (11)	0.053
Nervous system				
Hypotonia	14 (5)	14 (5)	1 (<1)	0.022*
Insomnia	28(10)	51 (19)	19 (12)	0.008*
Tremor	60 (21)	64 (24)	25 (16)	0.136
Respiratory system				
Epistaxis	8 (3)	13 (5)	1 (<1)	0.043*
Skin and appendages				
Acne	67 (24)	49 (18)	18 (11)	0.004*
Hirsutism	14 (5)	32 (12)	3 (2)	<0.001*
Rash	23 (8)	19 (7)	3 (2)	0.016*

*Overall difference among treatment groups assessed by Fisher's exact test.

Clinically important TEAE that occurred more frequently in Rapamune® treated patients compared to azathioprine treated patients include headache, lymphocele, hypertension, diarrhea, hypercholesteremia, hyperlipemia, hypotonia, epistaxis, acne, hirsutism, and rash. Leukopenia and insomnia occurred more frequently in the Rapamune® 5 mg/day group compared to the Rapamune® 2 mg/day group but not

compared to the azathioprine group. Thrombocytopenia occurred more frequently in the Rapamune® 5 mg/day group compared to either of the other two treatment groups. Hyperkalemia occurred more frequently in the Rapamune® 2 mg/day group compared to the Rapamune® 5 mg/day group but not compared to the azathioprine group. Anemia, hyperglycemia, increased creatinine, peripheral edema, arthralgia and tremor occurred with equal frequency in all treatment groups as did other less commonly reported events such as abnormal liver function tests, diabetes mellitus, TTP, and abnormal healing.

For this discussion, serious and clinically important adverse events are limited to patient death, graft loss, malignancy and life-threatening adverse events because of the number and severity of the adverse events that occur in the population of renal transplant patients. The numbers of patients with these events are summarized in Table 21.

Table 21
Summary of Deaths, Graft Loss, Malignancy, and Life-Threatening Adverse Events

Event	Rapamune® 2 mg/day (n=284)	Rapamune® 5 mg/day (n=274)	Azathioprine (n=161)
Death	3 (1.1)	8 (2.9)	3 (1.9)
Graft Loss	4 (1.4)	12 (4.3)	7 (4.3)
Malignancy	1 (0.4)	2 (0.7)	3 (1.9)
Life-Threatening Adverse Event	6 (2.1)	4 (1.5)	0

The deaths that occurred up through day 210 are presented in the above table. Fourteen patients died during this time. One patient died on day 209, outside of the 194-day interval encompassed by the 6-month efficacy analysis. Eleven of these 14 patients died with functioning renal allografts. Three patients died after experiencing graft loss. The incidence of patient death among treatment groups ranged between 1.1% and 2.9%. In the investigators' opinion, two patient deaths (1 in each Rapamune® treatment group) may have been related to the study medication. The causes of death were varied; most deaths were related to cardiovascular events (n=6), followed by infection (n=4), respiratory failure (n=2), hemorrhage (n=1), and lymphoma (n=1). There were no unusual or unexpected causes or rates of patient death during the six-month study period.

There were 34 patients who experienced graft loss during the first six months after randomization. The most common etiology of graft loss was death with a functioning graft (n=11), while 23 patients lost their renal allograft for various other reasons. The reasons for graft loss included vascular events, acute rejection, and acute tubular necrosis. Although the overall rate for the Rapamune® 2 mg/day group was lower, there did not appear to be unusual or unexpected causes or rates for graft loss.

Six patients had histologically confirmed malignancy during the first six months after randomization. Three of the six patients were randomized to the Rapamune® treatment

groups. However, the distribution of patients with malignancies was similar between treatment groups.

Thirteen patients had other non-fatal life-threatening adverse events during the first six months after randomization. The events were selected based upon being either an opportunistic infection, related to other safety concerns of Rapamune® administration, or being near fatal. Seven of the events were opportunistic infections with five of the seven patients having tuberculosis. The other events were occurrences of pulmonary embolism, intestinal perforation, pancreatitis, CVA, interstitial pneumonitis, and TTP. The relationship between these events and study drug administration is not established.

Laboratory parameters regarding renal function are also of interest. The applicant presented an analysis of GFR and serum creatinine at 12 months for only those patients still on therapy. An analysis that includes only patients still on therapy may eliminate a significant proportion of patients who had poor renal function. Since there were more rejections in the control group, this may unfavorably weight the analysis of the renal function parameters against Rapamune®. Thus, an FDA exploratory analysis was performed in an attempt to minimize any bias that may result because of this by using all patients who had a study visit at 12 months whether or not they had discontinued study drug. A study visit window of 337 to 393 days post transplant was used to determine a 12 month visit. Even though 11 to 14% of the study population (adjusted by excluding patients who died or had a graft loss) was still not included in the FDA analysis population, it was ensured that this population was representative to the overall study population by demonstrating similarity in the rates of rejection and the time to first rejection.

Table 22 summarizes the results of mean GFR and serum creatinine at 12 months for the FDA analysis population. Mean GFR and mean serum creatinine at 12 months is significantly better for patients treated with azathioprine than patients treated with either dose of Rapamune®.

Reviewer's Note: GFR is assessed using the calculated Nankivell GFR and is reported in cc/min. Serum creatinine is reported in mg/dL. Higher GFR values and lower serum creatinine values indicate better renal function.

Table 22
Mean (sd) GFR and Serum Creatinine at 12 Months

	Rapamune® 2 mg/day	Rapamune® 5 mg/day	Azathioprine
GFR (cc/min)	57.4 (19.6) n=233	55.1 (19.3) n=226	65.9 (19.0) n=127
p-value	0.0001	0.0001	
Serum Creatinine (mg/dL)	2.17 (1.49) n=233	2.09 (1.36) n=227	1.60 (0.63) n=127
p-value	0.0001	0.0002	

Since the differences in GFR and serum creatinine were in the opposite direction one would expect based on the differences in the rates of acute rejection, it became of interest to evaluate patients by their rejection status at 12 months. This would determine if there was an underlying difference independent of rejection.

Table 23 summarizes the mean GFR and serum creatinine separately for patients who had an acute rejection within the first 12 months and for those who did not have an episode of acute rejection. In all treatment groups, patients who had an episode of acute rejection had lower mean GFR and higher mean serum creatinine values at 12 months compared to patients without rejection. Whether or not a patient had an episode of acute rejection, mean GFR was significantly lower and mean serum creatinine was significantly higher for patients treated with either dose of Rapamune[®] compared to azathioprine.

Table 23
Mean (SD) GFR and Serum Creatinine at 12 Months
By Rejection Status

	Rapamune [®] 2 mg/day	Rapamune [®] 5 mg/day	Azathioprine
GFR (cc/min)			
Non-rejector	60.0 (18.1) n=187 p=0.0019	56.3 (19.0) n=199 p=0.0001	67.5 (19.6) n=95
Rejector	46.7 (22.0) n=46 p=0.001	45.7 (19.5) n=27 p=0.0019	61.1 (16.7) n=32
Serum Creatinine (mg/dL)			
Non-rejector	1.97 (1.29) n=186 p=0.0045	2.01 (1.35) n=201 p=0.0018	1.51 (0.60) n=95
Rejector	2.97 (1.94) n=47 p=0.0001	2.70 (1.34) n=26 p=0.0101	1.83 (0.66) n=32

Study 302

Of the 576 patients enrolled in the study, 550 received at least one dose of study medication and were valid for safety: 218 Rapamune[®] 2 mg/day patients, 208 Rapamune[®] 5 mg/day patients, and 124 placebo patients. One or more TEAEs that were not related to infection were reported during the on-treatment segment of the study by 212 (97%) Rapamune[®] 2 mg/day patients, 204 (98%) Rapamune[®] 5 mg/day patients, and 119 (96%) placebo patients. The most commonly occurring TEAE during the on-therapy period (reported in at least 20% of patients in any one treatment group) and the accompanying p-values are summarized by treatment group in Table 24.

Table 24
Number (%) of Patients Reporting Treatment Emergent Adverse Events ($\geq 20\%$)

Body system Event	Rapamune® 2 mg/day (n=218)	Rapamune® 5 mg/day (n=208)	Placebo (n=124)	p-value
Any adverse experience (1 or more)	212 (97)	204 (98)	119 (96)	0.491
Body as a whole				
Abdominal pain	50 (23)	57 (27)	25 (20)	0.292
Asthenia	33 (15)	43 (21)	22 (18)	0.317
Fever	35 (16)	51 (25)	26 (21)	0.087
Headache	55 (25)	57 (27)	23 (19)	0.184
Pain	58 (26)	36 (17)	23 (19)	0.053
Cardiovascular system				
Hypertension	80 (37)	84 (40)	51 (41)	0.611
Digestive system				
Constipation	75 (34)	69 (33)	35 (28)	0.507
Diarrhea	36 (16)	50 (24)	17 (14)	0.038*
Dyspepsia	43 (20)	40 (19)	30 (24)	0.506
Nausea	40 (18)	41 (20)	25 (20)	0.887
Hemic and lymphatic system				
Anemia	36 (16)	56 (27)	16 (13)	0.003*
Thrombocytopenia	25 (11)	47 (23)	4 (3)	<0.001*
Metabolic and nutritional				
Creatinine increased	56 (26)	65 (31)	40 (32)	0.295
Hypercholesteremia	81 (37)	91 (44)	25 (20)	<0.001*
Hyperkalemia	29 (13)	23 (11)	28 (23)	0.016*
Hyperlipemia	76 (35)	103 (50)	22 (18)	<0.001*
Peripheral edema	93 (42)	98 (47)	43 (35)	0.086
Musculoskeletal system				
Arthralgia	36 (16)	47 (23)	14 (11)	0.028*
Study event associated with miscellaneous factors				
Local reaction to procedure	79 (36)	78 (38)	40 (32)	0.633

*Overall difference among treatment groups assessed by Fisher's exact test.

Individual pairwise comparisons were performed for adverse events that were statistically significantly different among treatment groups. Significantly higher incidence rates in both Rapamune® doses compared to placebo were seen for thrombocytopenia, hypercholesteremia, and hyperlipemia. Hyperkalemia had significantly higher rates in the placebo group compared to either Rapamune® group. The rates of thrombocytopenia and hyperlipemia were also significantly higher in the Rapamune® 5 mg/day group than in the Rapamune® 2 mg/day group. The rate of anemia was significantly higher in the Rapamune® 5 mg/day group than either the Rapamune® 2 mg/day group or the placebo group. The rates of diarrhea and arthralgia were significantly higher in the Rapamune® 5 mg/day group than in the placebo group.

Table 25 lists the frequency of clinically important TEAE by treatment group.

Table 25
 Number (%) of Patients Reporting Clinically Important TEAE
 Excluding Infection and Malignancy

Body system Event	Rapamune® 2 mg/day (n=218)	Rapamune® 5 mg/day (n=208)	Placebo (n=124)	p-value
Body as a whole				
Headache	55 (25)	57 (27)	23 (19)	0.184
Lymphocele	20 (9)	25 (12)	6 (5)	0.091
Cardiovascular system				
Hypertension	80 (37)	84 (40)	51 (41)	0.611
Digestive system				
Diarrhea	36 (16)	50 (24)	17 (14)	0.038*
Endocrine system				
Diabetes mellitus	9 (4)	16 (8)	3 (2)	0.082
Hemic and lymphatic system				
Anemia	36 (16)	56 (27)	16 (13)	0.003*
Leukopenia	15 (7)	18 (9)	3 (2)	0.069
Thrombocytopenia	25 (11)	47 (23)	4 (3)	<0.001*
Thrombotic thrombocytopenia purpura (TTP) ¹	4 (2)	7 (3)	2 (2)	0.586
Metabolic and nutritional				
ALT increased	19 (9)	20 (10)	9 (7)	0.777
AST increased	9 (4)	15 (7)	6 (5)	0.369
Creatinine increased	56 (26)	65 (31)	40 (32)	0.295
Healing abnormal	15 (7)	22 (11)	7 (6)	0.224
Hypercholesteremia	81 (37)	91 (44)	25 (20)	<0.001*
Hyperglycemia	23 (11)	25 (12)	12 (10)	0.786
Hyperkalemia	29 (13)	23 (11)	28 (23)	0.016*
Hyperlipemia	76 (35)	103 (50)	22 (18)	<0.001*
Peripheral edema	93 (42)	98 (47)	43 (35)	0.086
Musculoskeletal system				
Arthralgia	36 (16)	47 (23)	14 (11)	0.028*
Nervous system				
Hypotonia	7 (3)	8 (4)	3 (2)	0.827
Insomnia	19 (9)	23 (11)	9 (7)	0.494
Tremor	33 (15)	35 (17)	14 (11)	0.391
Respiratory system				
Epistaxis	7 (3)	18 (9)	0	<0.001*
Skin and appendages				
Hirsutism	16 (7)	17 (8)	9 (7)	0.936
Rash	9 (4)	29 (14)	6 (5)	<0.001*

*Overall difference among treatment groups assessed by Fisher's exact test.

¹All patients with hemolytic uremic syndrome (HUS) were coded to this term.

Clinically important TEAE that occurred more frequently in Rapamune® treated patients compared to placebo treated patients include hypercholesteremia, hyperlipemia, and thrombocytopenia. Diarrhea, anemia, arthralgia, epistaxis, and rash occurred more frequently in the Rapamune® 5 mg/day group compared to either of the other two treatment groups. Hyperkalemia was reported more frequently in the placebo group than

in the Rapamune® groups. Headache, hypertension, increased creatinine, peripheral edema, and tremor were commonly reported, but these adverse events occurred with equal frequency in all treatment groups. Other less commonly reported events that also occurred with equal frequency in all groups included lymphocele, diabetes mellitus, leukopenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome (HUS), abnormal healing, hyperglycemia, abnormal liver tests, hypotonia, insomnia, and hirsutism.

Table 26 summarizes the number of patients with serious and clinically important adverse events; limited to patient death, graft loss, malignancy and life-threatening adverse events

Table 26
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	5 (2)	8(4)	6 (5)
Graft Loss	16 (7)	16 (7)	15 (12)
Malignancy	3 (1)	2 (1)	1 (1)
Life-Threatening Adverse Event	1 (<1)	2 (1)	1 (1)

Nineteen patients died within 6 months of randomization. Sixteen of these 19 patients died with functioning renal allografts. Two patients died after experiencing graft loss. The incidence of patient death among treatment groups ranged between 2.2% and 4.6%. In the investigators' opinion, seven patient deaths (2 in the Rapamune® 2 mg/day group, 4 in the Rapamune® 5 mg/day group, and 1 in the placebo group) may have been related to the study medication. The causes of death were varied; most deaths were related to infection (n=8) followed by cardiovascular events (n=6), hemorrhage (n=2), pulmonary embolism (n=1), cachexia (n=1), and multiple organ failure (n=1). There were no unusual or unexpected causes or rates of patient death during the 6-month study period.

There were 47 patients who experienced graft loss during the first six months after randomization. The most common cause of graft loss was death with a functioning graft (n=16), while 31 patients lost their renal allograft for various other reasons. The reasons for graft loss included vascular events, acute rejection, acute tubular necrosis, and infected graft. There were no unusual or unexpected causes or rates for graft loss.

Six patients developed biopsy-proven malignancy during the first six months after randomization. Five of the six patients were randomized to the Rapamune® treatment groups. However, the distribution of patients with malignancies was similar between treatment groups.

Four patients had other non-fatal life-threatening adverse events during the first six months after randomization. Two of these patients developed severe pneumonia due to infection with opportunistic organisms (*Aspergillus fumigatus*, CMV). One patient had multiple medical complications (myasthenia gravis, hemolytic uremic syndrome, intra-abdominal bleeding, and sepsis) and the other patient had complications following a severe retroperitoneal hemorrhage.

Table 27 summarizes the results of mean GFR and serum creatinine at 12 months for the FDA analysis population (see discussion in study 301 for description of the population). Mean GFR at 12 months is significantly better for patients treated with placebo than patients treated with either dose of Rapamune®. Mean serum creatinine values are not significantly different between either Rapamune® dose group and placebo.

Table 27
Mean (SD) GFR and Serum Creatinine at 12 Months

	Rapamune® 2 mg/day	Rapamune® 5 mg/day	Placebo
GFR (cc/min)	54.9 (17.4) n=190	53.0 (18.3) n=175	61.7 (18.2) n=101
p-value	0.0022	0.0001	
Serum Creatinine (mg/dL)	2.11 (1.65) n=191	2.11 (1.32) n=180	1.96 (1.77) n=102
p-value	0.4295	0.4357	

Table 28 summarizes the mean GFR and serum creatinine separately for patients who had an acute rejection within the first 12 months and for those who did not have an episode of acute rejection. In all treatment groups, patients who had an episode of acute rejection had lower mean GFR and higher mean serum creatinine values at 12 months compared to patients without rejection. Whether or not a patient had an episode of acute rejection, mean GFR was significantly lower for patients treated with Rapamune® 5 mg/day compared to placebo. For patients treated with Rapamune® 2 mg/day, only patients who had a rejection had significantly lower mean GFR compared to placebo. Regardless of rejection status, mean serum creatinine was not significantly different for patients treated with either dose of Rapamune® compared to placebo.

**APPEARS THIS WAY
ON ORIGINAL**

Table 28
Mean (SD) GFR and Serum Creatinine at 12 Months
By Rejection Status

	Rapamune® 2 mg/day	Rapamune® 5 mg/day	Placebo
GFR (cc/min)			
Non-rejector	57.3 (16.3) n=147 p=0.0329	55.2 (17.3) n=141 p=0.0038	62.9 (18.3) n=64
Rejector	46.8 (18.6) n=43 p=0.0012	43.5 (19.5) n=34 p=0.0001	59.7 (18.0) n=37
Serum Creatinine (mg/dL)			
Non-rejector	1.90 (1.22) n=148 p=0.7923	1.96 (1.12) n=145 p=0.5943	1.84 (1.62) n=65
Rejector	2.83 (2.53) n=43 p=0.0527	2.72 (1.83) n=35 p=0.1240	2.17 (2.02) n=37

APPEARS THIS WAY
ON ORIGINAL

Reviewer's Conclusions (which may be conveyed to the sponsor in the action letter)

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 azathioprine or placebo control groups during the first 6 months after transplantation.*
2. *The results of study 301 demonstrate equivalence, within a delta of 5%, of Rapamune® 2 mg/day and azathioprine in 1 year patient and graft survival rates. The results of study 302 demonstrate equivalence, within a delta of 5 to 10%, of Rapamune® 2 mg/day and placebo in 1 year patient and graft survival rates. Both Phase III studies demonstrate equivalence, within a delta of 5 to 10%, of Rapamune® 5 mg/day and comparator in 1 year patient and graft survival rates.*
3. *The results of both Phase III studies demonstrate equivalence, within a delta of 5%, of Rapamune® 2 mg/day and comparator in 1 year patient survival rates. Both Phase III studies demonstrate equivalence, within a delta of 5 to 10%, of Rapamune® 5 mg/day and comparator in 1 year patient survival rates.*
4. *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.*
5. *Overall, Rapamune® 2 mg/day and 5mg/day are relatively safe. Certain clinically important adverse events were reported more frequently in Rapamune® treated groups: arthralgia, diarrhea, epistaxis, hypertension, insomnia, lymphocele, laboratory abnormalities (hyperlipemia, hypercholesteremia, increased LDH, anemia, thrombocytopenia, leukopenia), peripheral edema, and rash. Most of these events occur more frequently in the Rapamune® 5 mg/day group compared to the Rapamune® 2 mg/day group.*

/S/

8/20/99

Cheryl Dixon, Ph.D.
Biostatistician, DOB III

/S/

8/20/99

Concur:

Nancy Silliman, Ph.D.
Team Leader, DOB III