U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDAs/Serial Number:	21-083 SE5-019
	21-110 SE5-024
Drug Name:	Rapamune® (sirolimus) Oral Solution and Tablets
Indication(s):	Prophylaxis of organ rejection in patients receiving renal transplants
Applicant:	Wyeth Pharmaceuticals
Date(s):	Stamp date: September 13, 2004
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	Review date: March 3, 2005
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
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Concurring Reviewer:	Mohammad Huque, Ph.D., Division Director
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Keywords: clinical studies, NDA review, renal transplant, pediatric exclusivity

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

No statistical differences between the sirolimus and standard therapy groups were observed for the primary efficacy endpoint of efficacy failure, a composite endpoint of the first occurrence of biopsy confirmed rejection, graft loss, or death. Therefore, the combination of sirolimus with a calcineurin inhibitor does not provide more effective prophylaxis against acute rejection or graft loss in the high risk subset of pediatric renal transplant patients enrolled in the study. However, the study fulfilled the requirements stated in the written request for pediatric exclusivity.

1.2 Brief Overview of Clinical Studies

One clinical study, Protocol 217, was submitted to fulfill a requirement stated in the pediatric written request to evaluate the safety and efficacy of sirolimus-containing regimen. Protocol 217 was a randomized, open label, comparative outpatient study in high-risk pediatric renal transplant subjects. Subjects were randomized in a 2:1 ratio to have sirolimus added to their calcineurin inhibitor regimen or to continue their current calcineurin inhibitor regimen. Two co-primary endpoints were stated in the written request. The first co-primary endpoint for efficacy was the first occurrence of biopsy-proven acute rejection, graft loss, or death (efficacy failure) after 36 months of treatment. The second co-primary endpoint for efficacy and safety was the patient and graft survival at 36 months.

1.3 Statistical Issues and Findings

A total of 102 patients were randomized, 65 patients to receive sirolimus and 37 to receive standard therapy. The rate of efficacy failure at 36 months was 44.6% for sirolimus and 32.4% for standard therapy. These rates were not significantly different. The study defined pediatric patients based on the NIH convention of < 20 years. The FDA definition of pediatric patients is < 18 years. Therefore, the subset of subjects < 18 years old consisted of 53 sirolimus patients and 25 standard therapy patients. The rate of efficacy failure at 36 months for this subgroup was 45.3% for sirolimus and 44.0% for standard therapy. As with the overall population, these rates were not significantly different. Patient and graft survival for the overall population was 73.8% for sirolimus patients and 83.8% for standard therapy patients. For subjects less than 18 years, patient and graft survival was 73.6 for sirolimus patients and 80.0% for standard therapy patients. These rates are not significantly different, however, non-inferiority based on a margin of 10% was not attained either.

This study did not enroll the planned sample size. Since enrollment of the study could not be completed, the study was inadequately powered to demonstrate statistically significant differences between treatment groups that may have existed.

2. INTRODUCTION

2.1 Overview

This is a supplemental NDA submission for Rapamune. Rapamune is approved for the prophylaxis of organ rejection in patients receiving renal transplants. A written request for a safety and efficacy study of a sirolimus-containing regimen in high-risk pediatric renal transplant patients and for pharmacokinetic evaluations in patients across various age groups was issued on September 15, 1999 and amended on May 17, 2004 and May 24, 2004. The purpose of this submission is to provide the pediatric study reports in fulfillment of the pediatric Written Request.

Two studies were performed in response to the Written Request, "An open label, comparative study of the effect of sirolimus versus standard treatment on clinical outcomes and histologic progression of allograft nephropathy in high risk pediatric renal transplant patients" (Protocol 217) and the pharmacokinetic portion of "A double blind randomized trial of steroid withdrawal in sirolimus and cyclosporine-treated primary transplant recipients" (Protocol 315). The focus of this review will be the clinical data provided in Protocol 217. For a discussion of Protocol 315, please refer to the Clinical Pharmacologist's review.

In August of 2001, the Division was notified by the sponsor that there was difficulty in enrolling patients into Protocol 217 for various reasons including: protocol mandated biopsies and blood draws and the fact that Rapamune was commercially available. Due to this difficulty in enrollment, the sponsor indicated that the study would not be able to be completed by deadline stated in the Pediatric Written Request. At that time, the Division agreed that the sponsor could submit the data from subjects enrolled up to a data cut-off date of June 2004 to allow them to meet the deadline for the study report stated in the written request. The sponsor informed the Division that 94 patients would have completed the 36 month follow-up by the June 2004 cut-off date. The Division informed the sponsor that although the study would satisfy the requirements stated in the written request, changes to the labeling, if any, may be limited.

2.2 Data Sources

The data analyzed in this review comes from the clinical study of high risk pediatric renal transplant patients. The Protocol 217 study report and datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\Cdsesub1\evsprod\n021083\0004.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Protocol 217 was designed as a randomized, open-label, comparative outpatient study in high-risk pediatric renal transplant subjects. The study was conducted at up 50 centers in the United States, Canada, and Mexico. Eligible subjects were those with 1 or more episodes of acute rejection as well as those subjects with biopsy-proven chronic rejection. Subjects were randomized in a 2:1 ratio to have sirolimus added to their calcineurin inhibitor regimen or to continue their current calcineurin inhibitor regimen. At randomization, subjects were stratified by the number of previous acute rejections ($\leq$1 or >1). Patients were to be followed for up to 36 months.

The primary objective of the study was to compare the safety and efficacy of sirolimus when added to a calcineurin inhibitor (cyclosporine [CsA] or tacrolimus) and corticosteroid regimen versus standard CsA or tacrolimus-based therapy in pediatric renal transplant subjects. The study had 2 related primary endpoints. Efficacy was to be assessed by comparing the composite endpoint of biopsy-proven rejection, graft loss, or death (efficacy failure) after 36 months of treatment. The primary analysis for this endpoint was time-to-event using Kaplan-Meier estimates and the statistical significance of differences between therapies was assessed by the log-rank test. Safety and efficacy was to be assessed by comparing the composite endpoint of graft loss or death after 36 months of treatment. The primary analysis for this endpoint was a 95% confidence interval about the difference in the rates of patient and graft survival (sirolimus - standard therapy). Secondary objectives included comparing efficacy failure after 6, 12, and 24 months; to determine the rate of clinically diagnosed (presumed) acute rejection at months 6, 12, 24, and 36; to determine the change in glomerular filtration rate (GFR) after 18 months of treatment; among others.

Patients were to be followed for 3 years on therapy followed by 1 month follow-up off therapy. The rate of efficacy failure (acute rejection/ graft loss/ death) was thought to be as high as 20% in this high risk population. Assuming a 2-sided significance level of 5%, a study with 142 patients receiving the sirolimus regimen and 71 patients receiving standard therapy would have 80% power to detect a 50% reduction in the hazard rate. With this sample size, the study would also be able to demonstrate non-inferiority with respect to patient and graft survival assuming a non-inferiority margin of 10% and a patient and graft survival rate of 90% by 3 years.

The study did not enroll the planned sample size. A total of 102 patients were randomized, 65 patients to receive sirolimus and 37 to receive standard therapy. This enrollment was approximately 50% of the planned enrollment. The effect of the truncated sample size was a reduction in the power of the study to detect the projected 50% reduction in the hazard rate of the efficacy failure endpoint and a decrease in the precision of the confidence interval of the difference in the rates of patient and graft survival. This power and precision are below the standards typically established for studies to support a new indication or use. Due to this, the

sponsor was informed that although the study would satisfy the requirements stated in the written request, changes to the labeling, if any, may be limited.

The primary efficacy analysis was based on the ITT (intent-to-treat) population. This population included all patients who were randomly assigned to treatment. All subjects who received at least 1 dose of study medication were included in the safety analysis. A secondary efficacy population that included subjects who received at least 21 days of study medication was also analyzed.

3.1.2 Patient Demographics

A total of 102 patients were randomized into the study and are included in the ITT population, 65 patients were randomized to receive sirolimus and 37 to receive standard therapy. Three patients (1 sirolimus and 2 standard therapy) never received study medication and were excluded from the safety population. Sixty-three sirolimus subjects and 35 standard therapy subjects received at least 21 days of medication. Since few subjects were excluded from the secondary efficacy population, this review will only discuss the efficacy results based on the ITT population.

Table 1 summarizes the demographic and baseline characteristics of the ITT population. There were no significant differences across treatment groups with the exception of age at study entry. The mean age of subjects who received standard therapy (15.4 years) was significantly higher than that of subjects who received sirolimus (12.8 years, p=0.006). Approximately two-thirds of the subjects were male and the majority was white. Most subjects received a living related donor organ. Approximately half of the subjects had ≤ 1 acute rejection prior to study entry.

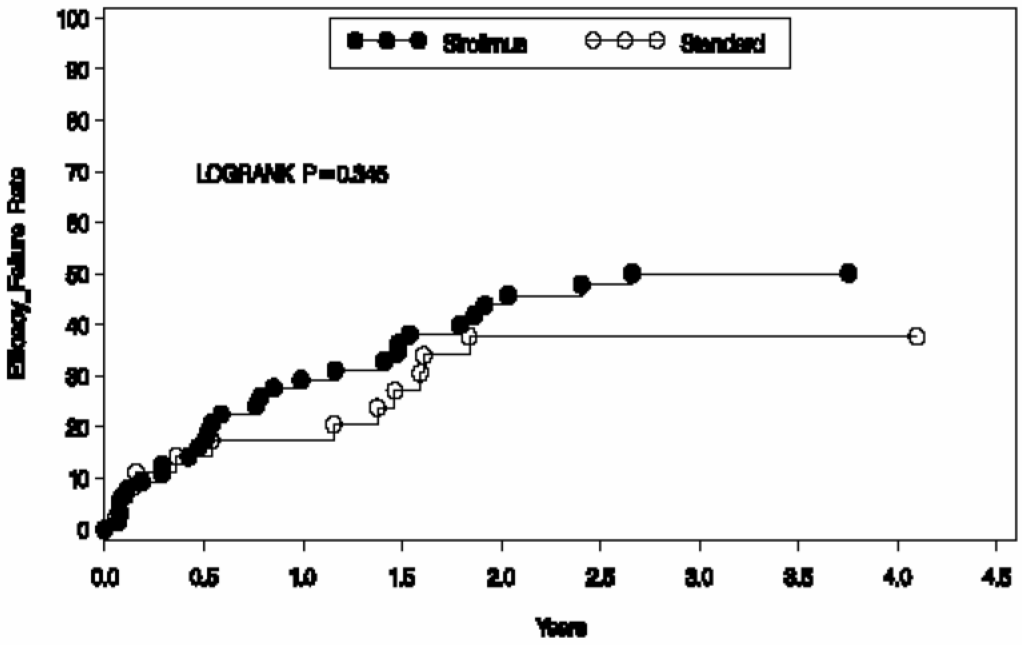
Table 1
Demographic and Baseline Characteristics (ITT)

	Treatment Group	
	sirolimus	**standard therapy**
# Patients	65	37
Gender		
Male	42 (64.6)	24 (64.9)
Female	23 (35.4)	13 (35.1)
Age mean (SD)	12.8 (4.7)	15.4 (4.0)
Min, max	2, 20	4, 20
Age groups at study entry		
0 to 5	4 (6.2)	1 (2.7)
6 to 11	20 (30.7)	4 (10.8)
12 to 17	29 (44.6)	20 (54.1)
≥18	12 (18.5)	12 (32.4)
Race		
White	55 (84.6)	32 (86.5)
Black	8 (12.3)	5 (13.5)
Native American	1 (1.5)	0
Other	1 (1.5)	0
Donor Source		
Cadaver	17 (26.2)	9 (24.3)
Living related	43 (66.2)	27 (73.0)
Living unrelated	5 (7.7)	1 (2.7)
Number of acute rejections before entry		
0 or 1	35 (53.9)	19 (51.4)
2 or more	30 (46.1))	18 (48.6)

3.1.3 Efficacy Results

Figure 1 shows the Kaplan-Meier plot of time to efficacy failure for the ITT population. The difference between the two curves was not statistical significant (log rank p-value=0.345). At 36 months, the cumulative efficacy failure rates were 50.2% for sirolimus and 37.8% for standard therapy.

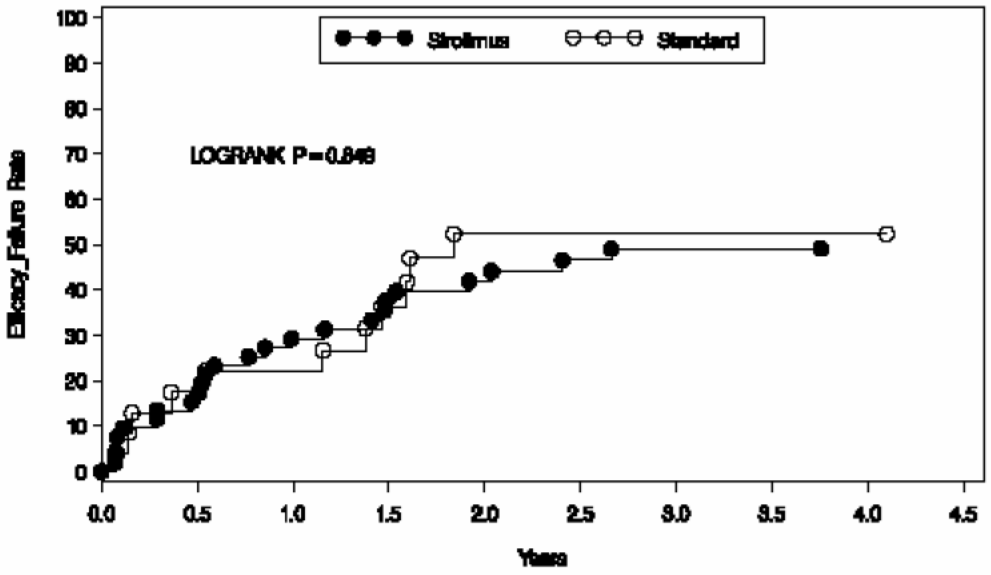
Figure 1
Time to Efficacy Failure (ITT population)



Source: Protocol 217 study report Figure 9.4.1.1-1

This study enrolled subjects up to 20 years of age. For the purposes of the written request, a pediatric patient is < 18 years of age. Figure 2 shows the Kaplan-Meier plot of time to efficacy failure for subjects in the ITT population who were less than 18 years. As with the overall population, the difference between the two curves was not statistically significant (log rank p-value=0.849). The cumulative efficacy failure rates at 36 months for subjects less than 18 years were 49.1% for sirolimus and 52.3% for standard therapy.

Figure 2
Time to Efficacy Failure (ITT population, Age < 18 years)



Source: Protocol 217 study report Figure 9.4.1.1-2

The results of efficacy failure at 36 months for the ITT population as a whole and for those subjects less than 18 years are presented in Table 2. The table also includes the rates for each component of the composite endpoint. The difference in the rates of efficacy failure was not statistically significant for either the ITT population or the subgroup of subjects < 18 years.

Table 2
Efficacy Failure at 36 months

		sirolimus	standard therapy	Difference and 95% CI*	p-value**
ITT	Overall rate	29/65 (44.6)	12/37 (32.4)	12.2 (-9.2, 33.6)	0.294
	Acute Rejection	19 (29.2)	7 (18.9)		
	Graft loss	10 (15.4)	5 (13.5)		
	Death***	0	0		
ITT, < 18 years	Overall rate	24/53 (45.3)	11/25 (44.0)	1.3 (-25.3, 27.9)	1.000
	Acute Rejection	16 (30.2)	6 (24.0)		
	Graft loss	8 (15.1)	5 (20.0)		
	Death***	0	0		

*A difference (sirolimus- standard) greater than zero favors the standard therapy. The 95% CI is calculated using the normal approximation to the binomial with continuity correction.
**Fisher's Exact test
***Although 1 subject in each treatment group died, both had graft loss before they died and are counted under graft loss.

Patient and graft survival at 36 months is presented in Table 3. Patient and graft survival for the ITT population was 73.8% for sirolimus patients and 83.8% for standard therapy patients. For subjects less than 18 years, patient and graft survival was 73.6% for sirolimus patients and 80.0% for standard therapy patients. These rates are not significantly different, however, non-inferiority based on a margin of 10% was not attained either. All cases of graft loss were

due to pure graft loss and not death with a functioning graft. One subject in each group did died but following a graft loss.

Table 3
Patient and Graft Survival at 36 months

	Sirolimus	Standard therapy	Difference and 95% CI*
ITT	48/65 (73.8)	31/37 (83.8)	-10.0 (-28.1, 8.1)
ITT, < 18 years	39/53 (73.6)	20/25 (80.0)	-6.4 (-29.0, 16.2)

*A difference (sirolimus- standard) greater than zero favors sirolimus. The 95% CI is calculated using the normal approximation to the binomial with continuity correction.

3.2 Evaluation of Safety

A total of 50 patients (76.9%) in the sirolimus group and 27 patients (73.0%) in the standard therapy group had at least one clinical adverse event. Serious adverse events were reported in 35 (53.8%) sirolimus patients and 15 (40.5%) standard therapy patients. There were 2 deaths in the study: 1 in the sirolimus arm due to sepsis after discontinuation for acute rejections and 1 in the standard therapy arm due to a cerbrovascular accident in a subject with a nonfunctioning graft.

A total of 23 subjects experienced graft losses, 17 (26.2%) in sirolimus treated patients and 6 (16.2%) in the standard therapy group. None of the graft losses were due to death with a functioning graft. One patient in each group subsequently died and the remaining 21 subjects with graft loss remain alive. The predominant cause of graft loss was chronic rejection (15 out of 17 sirolimus and 1 out of 6 standard therapy).

Four subjects had a confirmed malignancy, 2 in each treatment group. No instances of basal or squamous cell carcinoma were reported.

For a detailed review of the safety data, please see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

There was no significant difference in efficacy failure rates by gender when compared to the overall study population. The majority of the subjects in this study were white (85%). Therefore, differences due to race cannot be assessed using this data. The study was conducted in pediatric patients less than or equal to 20 years. A subgroup analysis based on patients <18 years has already been discussed in Section 3.1.3. The majority of these patients were between 6 and 17 years so no additional age group analyses would provide informative comparisons.

4.2 Other Special/Subgroup Populations

Subjects were stratified at baseline by the number of previous acute rejections (≤ 1, 2 or more). There was no significant difference in efficacy failure rates by the number of previous acute rejections when compared to the overall study population.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Since enrollment of the study could not be completed, the study was inadequately powered to demonstrate statistically significant differences between treatment groups that may have existed. The rate of efficacy failure at 36 months in the subset of subjects less than 18 years was numerically similar between the sirolimus and standard therapy groups although there is a slight trend in favor of the standard therapy for patient and graft survival at 36 months.

5.2 Conclusions and Recommendations

No statistical differences between the sirolimus and standard therapy groups were observed for the primary endpoint of efficacy failure, a composite endpoint of the first occurrence of biopsy confirmed rejection, graft loss, or death. Therefore, the combination of sirolimus with a calcineurin inhibitor does not provide more effective prophylaxis against acute rejection or graft loss in the high risk subset of pediatric renal transplant patients enrolled in the study. However, the study fulfilled the requirements stated in the written request for pediatric exclusivity.

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