

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-110

MEDICAL REVIEW

Medical Officer's Review

NDA 21-110
Submitted: October 29, 1999
Review completed: August 18, 2000

Drug name: Sirolimus
Generic name: Sirolimus
Proposed trade name: Rapamune™

Chemical name: 21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentrione-1,5,11,28,29 (4H,6H,31H)-pentone

Sponsor: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

Pharmacologic Category : Immunosuppressant

Proposed Indication(s): Prophylaxis of rejection in renal transplantation

Dosage Form(s) and Route(s) of Administration: 1 mg tablet, 2mg/day dose
oral

NDA Drug Classification: 3S

Related Reviews: Biostatistics dated August 21, 2000
Biopharmaceutics dated
Pharmacology-Toxicology dated
Chemistry dated

EXECUTIVE SUMMARY

Rapamune® Oral Solution was approved September 15, 1999 (NDA 21-083).

Rapamune® Oral Solution, when administered with cyclosporine and steroids, has been shown to be safe and effective in the prophylaxis of organ rejection in patients receiving renal transplants. A tablet formulation of sirolimus has now been developed. The results of the bioequivalence study in normal healthy subjects indicate that the solid formulation has a lower peak concentration (C_{max}) and longer time to peak concentration (T_{max}) than the liquid formulation. The data suggest that the area under the blood concentration-time curve (AUC) for the solid formulation is approximately 27% greater than that for the liquid formulation. The two sirolimus formulations were not found to be bioequivalent. Consequently, pivotal study 309 was initiated as an open label, randomized, clinical trial comparing sirolimus tablet to sirolimus oral solution in order to assess whether these differences in pharmacokinetic parameters might result in unacceptable differences in immunosuppressive activity or in safety profiles.

Conclusions regarding Efficacy and Safety:

1. Overall, the Rapamune® Oral Solution and tablet formulations have similar efficacy and safety profiles. No clinically important adverse events were reported more frequently in the tablet formulation. The adverse event profile continues to include the following entities: hypercholesterolemia, hypertriglyceridemia, thrombocytopenia, anemia, leukopenia, elevated creatinine and decreased glomerular filtration rate (GFR). In addition, cases of interstitial pneumonitis occurring in patients taking Rapamune® oral solution have been reported to FDA. Consequently, pneumonitis should be included in the list of adverse events.
2. Although the 2 mg/day dose of Rapamune® tablet and the 2 mg/day dose of Rapamune® oral solution are not bioequivalent, they are clinically equivalent. However, we do not have information regarding the clinical equivalence of tablet doses higher than 2 mg/day. There are no clinical or pharmacokinetic data to support the interchangeable use of the 5 mg dose of Rapamune® oral solution with a 5 mg dose of Rapamune® tablet.

Recommendations:

The 2 mg/day oral dose of Rapamune® tablet should be approved for the prophylaxis of organ rejection in patients receiving renal transplants. The interchangeability of higher doses of Rapamune® oral solution and tablet has not been established.

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4. Material Reviewed

NDA Index and Summary sections in Vol.1: 1.1-1.3, the electronic version of Vol. 55, the electronic case report forms (CRF) and electronic case report tabulations (CRT), the 4-month Safety Update Report dated February 29, 2000, and the electronic regulatory reviewer aids dated October 1999 and April 2000 containing the NDA paper volumes and PDF files and SAS XPT files of the statistical data.

5.0 Chemistry/Manufacturing Controls

Please refer to the Chemistry review for additional details.

6.0 Animal Pharmacology/Toxicology

Please refer to the Pharmacology-Toxicology for additional details.

7.0 Clinical Background

7.1 Relevant Human Experience

Rapamune[®] Oral Solution, approved September 15, 1999, has been shown to be safe and effective in the prophylaxis of organ rejection in patients receiving renal transplants. A tablet formulation of sirolimus has now been developed. The tablet formulation has several advantages over the oral solution formulation in terms of convenience for the patient. Unlike the solution, the tablet can be stored at room temperature and does not require reconstitution. The tablet, however, is not bioequivalent to the oral solution. Consequently, data has been submitted to demonstrate the clinical comparability of the two dosage forms. This NDA seeks approval of the tablet-dosage form for the same indication as the approved oral solution.

7.2 Important information from related INDs and NDAs

Rapamune[®] Oral Solution (NDA 21-083) at a dose of 2 mg/day was approved for the prevention of organ rejection following renal transplantation on September 15, 1999. Sirolimus oral solution was assessed in two randomized, double-blind, multicenter, controlled trials in which 1,295 patients were enrolled. These studies compared the safety and efficacy of two dose levels of sirolimus oral solution (2 mg and 5 mg once daily) with azathioprine or placebo when administered in combination with cyclosporine and corticosteroids for the prevention of renal allograft rejection.

In these studies, adverse events that occurred significantly more frequently in the sirolimus groups in a dose-dependent manner (more so at the higher dose) than in either control group included: diarrhea, facial edema, dysuria, chills, fever, back pain, hypotension, lymphocele, herpes simplex infections, hirsutism, thrombotic thrombocytopenic purpura (TTP), ecchymosis, increased LDH, insomnia, thrombocytopenia, leukopenia, anemia, hypokalemia and hypertriglyceridemia. A

significant number of patients developed new onset hypercholesterolemia and hypertriglyceridemia and required lipid-lowering medications.

7.3 Foreign Experience

Reviewer's note: *To date, Rapamune® oral tablet has not been approved anywhere else in the world.*

7.4 Human Pharmacology, Pharmacokinetics (pK), Pharmacodynamics

Please refer to the Biopharmaceutics Review for additional details.

The following is a summary of the relevant pharmacokinetic information. A tablet formulation of sirolimus has now been developed; the results of preliminary studies in normal healthy volunteers indicate that the solid formulation has a lower peak concentration (C_{max}) and longer time to peak concentration (T_{max}) than the liquid formulation, and data suggest that the area under the blood concentration-time curve (AUC) for the solid formulation is approximately 27% greater than that for the liquid formulation. Because the two formulations are not bioequivalent, it was important to undertake studies to assess whether these differences in pharmacokinetic parameters might result in differences in immunosuppressive activity or in safety profiles.

The pivotal study 309 included in this application was designed to compare the efficacy, and to determine the pharmacokinetic profiles of sirolimus oral liquid and sirolimus tablets in *de novo* kidney transplant recipients.

Results of the study found that mean whole blood sirolimus trough concentrations, in renal transplant patients receiving either Rapamune® oral solution or Rapamune® tablets with a loading dose of three times the maintenance dose, achieved steady-state concentrations within 24 hours after the start of dose administration. Whole blood sirolimus trough concentrations (mean \pm SD), as measured by immunoassay, for the 2 mg oral solution and 2 mg tablet over 6 months, were 8.94 ± 4.36 ng/mL ($n=172$) and 9.48 ± 3.85 ng/mL ($n=179$), for the oral solution and oral tablet, respectively.

Reviewer's note: *In pivotal study 309, information regarding whether patients took the medication with or without food was not available and a variety of different practices could have been followed. This raises concern whether food intake could contribute to variability in exposure to sirolimus and, thus, mask differences between treatment groups. Consequently, the package insert should continue to recommend that Rapamune® oral solution and tablet be taken consistently either with or without food. It should also be noted that because sirolimus has a long plasma half-life, the effect of day to day changes in compliance may be less problematic.*

The mean bioavailability of sirolimus after administration of the tablet relative to the oral solution is increased by 27%. Variability in AUC was noted to be 40% in patients

receiving the sirolimus tablet and 28% variability in AUC was noted in patients receiving sirolimus oral solution.

Reviewer's note: Overall, exposure to sirolimus is expected to be slightly higher in renal transplant patients who receive the tablet compared to those who receive the oral solution. The difference in exposure of renal transplant patients to sirolimus when Rapamune® is administered as a tablet compared to an oral solution has not been evaluated at doses greater than 2 mg/day.

Please see the Biopharmaceutics review for further information regarding any differences in the pK and variability in exposure to Rapamune® which were identified in patients treated with Rapamune® oral solution when compared to Rapamune® tablet.

7.5 Description of Clinical Data Sources

This application is supported by a single large clinical study entitled "COMPARATIVE STUDY OF THE EFFECT AND EQUIVALENCE OF SIROLIMUS ORAL LIQUID VERSUS SIROLIMUS TABLETS, ADMINISTERED CONCOMITANTLY WITH CYCLOSPORINE AND CORTICOSTEROIDS IN RENAL ALLOGRAFT RECIPIENTS" Protocol 0468H1-309-GL-GMR-34966. This study was designed to evaluate the clinical equivalence of Rapamune® tablet to Rapamune® oral solution, and assess whether the two formulations could be used interchangeably at a dose of 2 mg per day. This was a randomized, open-label, dose-controlled, comparative study that was conducted at 30 centers in Australia, Canada, and the United States. The study enrolled 457 patients. Children less than or equal to 13 years of age were not eligible to participate in this study of the sirolimus tablet. Pediatric trials, using sirolimus oral solution, are currently ongoing.

Reviewer's note: The size and duration of pivotal study 309 are adequate to evaluate the safety and efficacy of the sirolimus tablet in adults. The study was designed to adequately collect adverse event data. The safety summary and 4 month safety update specifically address the known toxicities of sirolimus such as hyperlipidemia. Additional phase I clinical pharmacology studies in smaller numbers of subjects and for shorter duration are also included in this application. These are considered in the Biopharmaceutical review and will not be mentioned any further in this review.

8.0 Applicant's protocol 0468H1-309-GL GMR-34966

8.1 Objective

The primary objective of the study is to compare the efficacy and to investigate the equivalence of sirolimus oral liquid (the approved 2 mg/day dose) and sirolimus tablets (2 mg/day dose) administered concomitantly with cyclosporine and corticosteroids to *de novo* renal allograft recipients. Efficacy was assessed by a composite endpoint of the

incidence of first biopsy-confirmed acute rejection episode, graft loss, or death during the first 3 months after transplantation.

Reviewer's Note: *The approval of sirolimus oral solution (NDA 21-083) was based upon efficacy failure at 6 months and patient and graft survival at 1 year as co-primary endpoints. Study 309 was designed to utilize efficacy failure at 3 months, along with 12-month patient and graft survival, to assess the activity of the two formulations of sirolimus. The 3-month endpoint was considered to be a valid assessment of efficacy because the highest incidence of acute rejection occurs within the first 3 months after transplantation. At the pre-NDA telephone conference held on April 7, 1999, the Division stated that the 6-month efficacy failure endpoint would be considered along with the 3-month efficacy failure and 12-month patient and graft survival endpoints.*

There were several issues that led to the acceptability of the open-label nature of this study. There was no preliminary efficacy data with the tablet formulation prior to the start of the study. Thus, there was reluctance on the part of the study investigators to participate in a double-dummy design trial. In the majority of the cases, the same study centers and investigators who participated in the phase III pivotal studies for the oral solution also conducted study 309. The primary endpoint (acute rejection, graft loss, or death) was composed of well-established, objective, clinically relevant variables, unlikely to be affected by patient or investigator bias. Further, the diagnosis of acute rejection required biopsy confirmation by a trained pathologist who was blinded to patient treatment assignments.

Reviewer's note: *Investigator bias may be present in an open-label study. This may impact patient management and the interventions rendered. However in this study, I do not believe that investigator bias played a major role or affected the overall efficacy or safety outcomes of the study. In addition, the Applicant is not making any comparative competitive claims.*

8.2 Protocol

This was a randomized, open-label, dose-controlled, comparative study that was conducted at 30 centers in Australia, Canada, and the United States.

Reviewer's note: *The Division of Scientific Investigations evaluated two U.S. study sites and found no major discrepancies that would compromise either the quality or integrity of the safety and efficacy data.*

Pre-study screening/baseline evaluations were performed within 1 week before transplantation. Written informed consent was obtained before screening. Patients were randomly assigned before transplant surgery to receive either the solution or tablet formulations of sirolimus. Their assigned treatment began within 24 to 48 hours after renal transplantation.

Reviewer's note: Because randomization occurred prior to transplantation, one would anticipate a greater enrollment of patients with delayed graft function (DGF) when compared to enrollment in a protocol that randomizes after transplant surgery.

Patients who met eligibility criteria were randomly assigned in a 1:1 allocation to one of two treatment groups and began their assigned treatment. In the event of acute tubular necrosis (ATN) or delayed graft function (DGF), patients were permitted to receive antilymphocyte antibody preparations (OKT-3®, antilymphocyte globulin, antithymocyte globulin), Prograf® and CellCept® along with sirolimus until renal function improved and cyclosporine therapy could be initiated. Sirolimus administration, concomitant to antilymphocyte antibody therapy for the treatment of acute rejection, was also permitted. However, planned induction therapy with antilymphocyte antibody preparations was not permitted.

Reviewer's note: Treatment of delayed graft function and ATN using antilymphocyte preparations was allowed in this study. There was no major difference reported in the use of antilymphocyte preparations in the treatment of DGF across treatment arms that would have impacted the efficacy or safety results.

Patients were discharged from the hospital following the standard postoperative course and returned for follow-up evaluations at designated time points. Patients were evaluated for the primary study endpoint after 3 months of therapy but continued to receive sirolimus for up to 12 months. The total study duration was approximately 2 years (10-month enrollment period, 12-month treatment period, 3 month follow-up period). After completion of the treatment period, patients had a physical examination (including weight and vital signs) and determination of serum creatinine and serum BUN or urea levels at month 15. Adverse events were recorded up to month 15.

Protocol Deviations

There were no systematic deviations from the protocol that affected the outcome of this study

Reviewer's note: It is important to note that patients who were undergoing a second renal transplant were allowed to enroll in this trial. The numbers of patients who enrolled in the trial and had a primary or secondary renal transplant were equally balanced between the two treatment arms. Only one patient had a tertiary transplant and this patient randomized to the sirolimus tablet arm.

8.3 Procedures

Administration of Study Medication:

Treatments Administered

Patients were randomly assigned to one of two groups: group A (sirolimus oral

solution 2 mg/day) and group B (sirolimus tablet 2 mg/day). Each group received cyclosporine microemulsion and corticosteroids.

Group A: Sirolimus Oral Solution

Initial loading dose: 6 mg

Maintenance dose: 2 mg/day

Group B: Sirolimus Tablets

Initial loading dose: 6 mg

Maintenance dose: 2 mg/day

In groups A and B:

1. Cyclosporine microemulsion was administered as per standard local practice at each study center.
2. The first dose of sirolimus was administered between 24 to 48 hours after transplant surgery.
3. Sirolimus oral solution was administered either PO or NG
4. Sirolimus loading dose was not administered within 4 hours of cyclosporine.
5. Sirolimus maintenance doses were administered 4 hours after the morning dose of cyclosporine.
6. Corticosteroid therapy was initiated within 24 hours before or after transplantation. Corticosteroids were administered as per standard local practice to achieve a maintenance dose of 5 to 10 mg/day by the end of the 3rd month after transplantation. At the discretion of the investigator, the corticosteroid dosage was tapered and treatment discontinued after completion of 6 months of therapy.

Reviewer's note: This NDA 21-110 differs from the sirolimus oral solution NDA 21-083, in that investigators were allowed to discontinue steroid therapy at 6 months post-transplant. There was no significant difference between treatment groups in the frequency of the non-study immunosuppressive medications, except for greater use of corticosteroids in the sirolimus solution patients post-study. Ninety-six percent (96%) of patients in the sirolimus solution arm and 83% in the sirolimus tablet arm were on corticosteroids post-study. This did not impact the efficacy outcome at 6 months and did not appear to impact patient and graft survival at one year. Almost all of the graft losses occurred before 6 months except for two patients, one in each study arm, who lost their graft due to non-compliance with their immunosuppressive regimen.

Therapy permitted during the treatment period:

1. Therapies for other preexisting medical conditions.
2. Antilymphocyte antibody therapy for the treatment of postoperative ATN/DGF and acute rejection.
3. Standard perioperative and postoperative drug regimens.
4. If required, antacids were administered a minimum of 2 hours before or after administration of sirolimus.

Reviewer's note: Prophylaxis for pneumocystis carinii (PCP), cytomegalovirus (CMV) and oral candidiasis was adequate and similar across treatment groups.

Concomitant medications

The use of multiple concomitant therapies is common in renal transplant patients and in this study was frequent in both treatment groups and followed the expected patterns for this patient population. Drugs concomitantly used included anti-infectives (antibiotics and antivirals) anilides, calcium channel blockers, combined and plain sulfonamides and H₂-receptor antagonists and lipid-lowering agents.

Reviewer's note: *There were no significant differences in the use of fibrates, HMG-CoA reductase inhibitors or other non-study medications between the two sirolimus treatment arms.*

8.4 Co-primary Endpoints

As stated in the protocol, the first co-primary endpoint was efficacy failure in the first 3 months (≤ 104 days) after transplantation. Efficacy failure was defined as the first occurrence of biopsy-confirmed acute rejection, graft loss necessitating maintenance dialysis for >56 days) or death. The second prospectively defined co-primary endpoint was patient and graft survival at one year.

The following is taken from the FDA biostatistical review.

Prospectively defined secondary endpoints were incidence of biopsy-confirmed acute rejection, graft function (measured by serum creatinine and calculated creatinine clearance), incidence of documented infection or presumptive infection analyzed, and the incidence of histologically confirmed lymphoproliferative disease or other malignancy. The above secondary endpoints were all analyzed at 3, 6 and 12 months after transplant. Efficacy failure at 6 and 12 months after transplant was considered as "other descriptive analyses" in the protocol.

Reviewer's Note: *The approval of sirolimus oral solution was based upon efficacy failure at 6 months and patient and graft survival at 1 year as co-primary endpoints. Study 309 was designed to utilize efficacy failure at 3 months, along with 12-month patient and graft survival, to assess the activity of the two formulations of sirolimus. The 3-month endpoint was considered to be a valid assessment of efficacy because the highest incidence of acute rejection occurs within the first 3 months after transplantation. At the pre-NDA teleconference held on April 7, 1999, the Division stated that the 6-month efficacy failure endpoint would be considered along with the 3-month efficacy failure and 12-month patient and graft survival endpoints.*

It was considered acceptable to conduct study 309 as an open-label protocol because the primary endpoint (acute rejection, graft loss, or death) was composed of well-established, objective, clinically relevant variables, unlikely to be affected by patient or investigator bias. In addition, the diagnosis of acute rejection required biopsy confirmation by a trained pathologist who was blinded to patient treatment assignments.

Reviewer's note: *The evaluation of acute rejection utilizes a standardized histologic grading system [redacted] and was a strength of this study.*

8.5 Statistical Considerations

Please refer to the Statistical Review from which the following information has been taken.

Efficacy Evaluation

The primary analysis of efficacy failure consisted of calculating a two-sided 95% confidence interval around the differences in rates for the two formulations (tablet – oral solution). All patients assigned to treatment were included in this analysis. Equivalence of the tablet to the oral solution is demonstrated if the 95% confidence interval crosses zero and remains within a pre-defined upper bound (i.e., if the rate of the endpoint for the tablet formulation did not exceed the oral solution by more than a fixed number of percentage points). The upper bound of the confidence interval was chosen on the basis of the efficacy of the oral solution. The more efficacious the oral solution, the more stringent the definition of equivalence. The prospective definition of equivalence stated by the Applicant is:

Table 1

Definitions of Equivalence		
If the rate of the efficacy endpoint for the oral solution is greater than:	But less than or equal to:	The upper bound of the CI* will be no greater than:
0%	10%	10%
10%	20%	15%
20%	30%	20%

*: The 95% confidence interval of the difference in rates of the tablet minus the oral solution.

Statistical Reviewer's Note: *Regardless of the rate of the endpoint for the oral solution, the Division would prefer a delta of no more than 10% in assessing the equivalence of transplant products.*

Similarity with respect to patient and graft survival incidence rates was assessed with confidence intervals about the difference in rates (tablet – oral solution). 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® tablets.

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.

8.6 Disposition of Patients

Study 309 was conducted in 30 centers in the United States, Europe and Australia.

Reviewer's note: The Division of Scientific Investigation (DSI) visited two study sites in the United States and found no major discrepancies that would exclude the use of data from any of the sites in the final analysis.

Four hundred seventy-seven (477) patients were enrolled in the study; 238 were randomly assigned to sirolimus solution treatment and 239 were assigned to sirolimus tablet treatment, and were evaluated for efficacy. Four hundred fifty-seven (457) patients received at least one dose of study medication. Nine (9) patients who randomized to solution and 11 patients who randomized to tablet received no study medication (see Table 2 below)

Table 2 Patient Accounting by Treatment Group Study 309

Study 309	Sirolimus (SRL) Solution	Sirolimus (SRL) Tablet
Patients randomized	238	239
Patients enrolled	229	228

The reasons these patients were withdrawn from the study are listed in Table 3. The most common reason cited for withdrawal before receiving study medication was protocol violation such as planned induction therapy with antilymphocyte antibody preparations.

Reviewer's note: If DGF and ATN developed post-transplant, investigators were allowed to administer anti-lymphocyte therapy. However, planned induction, using antilymphocyte therapy, was prohibited.

TABLE 3 PATIENTS RANDOMIZED INTO STUDY WHO DID NOT RECEIVE ANY STUDY MEDICATION

Patient Number	Reason for for Discontinuation	Verbatim Reason Discontinuation
Sirolimus Solution (n=9)		
309C5-2506	Other nonmedical event	Compliance issue
309C6-2605	Patient request	Patient changed his mind
309C9-2903	Protocol violation	Required antilymphocyte therapy for induction
309C9-2906	Protocol violation	Required antilymphocyte therapy for induction
309C9-2907	Protocol violation	Required antilymphocyte therapy for induction
309C9-2910	Protocol violation	Required antilymphocyte therapy for induction
309D1-3119	Protocol violation	Prostate cancer less than 10 years before study
309E0-4050	Protocol violation	Raised lipids ineligible for study

309E0-4054	Protocol violation	Patient required prohibited medication
Sirolimus Tablet (n=11)		
309A8-0808	Protocol violation	Patient unstable during/after transplant; physician decision not to medication
309B5-1507	Other nonmedical event	Physician request
309B5-1510	Other nonmedical event	Physician request
309B8-1801	Protocol violation	Dilantin therapy
309C1-2103	Patient request	Patient decided not to participate
309C1-2114	Adverse event	Death
309C2-2205	Protocol violation	OKT-3 was given intra-op
309C2-2212	Protocol violation	Patient had history of myocardial infarction
309C2-2215	Patient request	Patient changed his mind and wants to withdraw from the study
309C6-2610	Protocol violation	Low platelet count – patient did not meet inclusion criteria
309D9-3965	Protocol violation	Patient already enrolled in another study

Reviewer's note: The numbers of patients who were randomized and did not receive study medication were reasonably small and appeared to be evenly distributed between the two treatment groups. These patients were included in the three and six month primary analyses of efficacy and were evaluated according to their intent-to-treat assignment. Twelve month follow-up for patient and graft survival was also obtained on these twenty patients who randomized and failed to enroll.

Over the course of the 12 month treatment period following transplantation, several patients discontinued study medication. Discontinuation was defined as having study drug held for ≥ 21 days. The most frequent reason for discontinuation in both sirolimus treatment groups during the first 12 months (dosing phase) was discontinuation for adverse reaction. Patients who discontinued sirolimus therapy before completing 12 months of treatment were not to be replaced, regardless of the reason. Follow-up information and the date of discontinuation of sirolimus use were to be recorded on the patient's case report form (CRF). Adverse events were to be recorded at the time of discontinuation of sirolimus therapy, through 1 month after discontinuation of sirolimus use. Limited adverse event recording (including infections and malignancies) were to occur at 3, 6, and 12 months after transplantation. Patient and graft survival were evaluated at the time of discontinuation of sirolimus therapy and at 3, 6, and 12 months after transplantation.

For each treatment group, Table 4 shows, by reason, the number of patients who discontinued drug therapy during the first 12 months after transplantation.

Table 4 Patients who discontinued during the treatment phase

Reason	Sirolimus oral solution (n= 229)	Sirolimus tablet (n=228)	Fisher's exact p-value
Adverse reaction	38 (17)	41 (18)	0.712
Failed to return	3 (1)	0	0.248
Non-medical event	4 (2)	4 (2)	1.00
Patient request	8 (3)	4 (2)	0.381
Protocol violation	0	2 (<1)	0.248
Unsatisfactory response/efficacy	22 (10)	22 (10)	1.00
Total # discontinuations	75 (33)	73 (32)	

Reviewer's note: The most frequent reason for discontinuation during the initial 12 month study period was adverse reaction (17% in the solution group compared to 18% in the tablet group.) The rates of discontinuation for adverse events in study 309 were similar across treatment arms. Patients who discontinued study drug were included in the 3 and 6 month efficacy analyses and evaluated according to their intent-to-treat study drug assignment.

It should also be noted that in each treatment arm, after completing 12 months of therapy, approximately 50% of the study patients on sirolimus oral solution (115 patients) and 51 % of the patients on sirolimus tablet (117 patients) discontinued treatment because they were transferred to maintenance studies where they continued on sirolimus.

Table 5 shows demographic and baseline characteristics for all randomized patients. There were no statistically significant differences between the treatment groups. The majority of the patients were male and Caucasian. The source of the donor allograft was primarily cadaveric. The descriptive variables, which include gender, race, and donor source, were evaluated using CMH tests stratified by investigator. Age was evaluated using ANOVA with treatment and investigator as factors.

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**Table 5
Patient Demographics¹**

	Sirolimus Oral Solution	Sirolimus Tablets	P-value
# Patients	238	239	-
Gender N (%)			0.830
Female	95 (39.9)	93 (38.9)	
Male	143 (60.1)	146 (61.1)	
Age mean (SD)	44.6 (12.8)	46.0 (13.0)	0.216
Min, max	17, 70	16, 74	
Race N (%)			0.921
Caucasian	140 (58.8)	137 (57.3)	
Black	54 (22.7)	59 (24.7)	
Hispanic	24 (10.1)	22 (9.2)	
Oriental (Asian)	9 (3.8)	12 (5.0)	
Other	11 (4.6)	9 (3.8)	
Donor Source N (%)			0.571
Cadaver	158 (66.4)	170 (71.1)	
Living (Related)	55 (23.1)	49 (20.5)	
Living (Unrelated)	25 (10.5)	20 (8.4)	

1. FDA statistical reviewer's analysis.

Reviewer's note: *There were no significant differences across treatment arms regarding gender, age, race, donor source or second transplant/"re-transplant" status. There was adequate representation of women, Black, Asian and Hispanic patients.*

Baseline Characteristics

The most common etiologies of renal failure were hypertension and glomerulonephritis, followed by diabetes mellitus.

Reviewer's note: *The main etiologies for renal failure in this study are representative of the reasons for end-stage renal disease in the United States population and were balanced across treatment arms.*

8.7 Efficacy Evaluation

The following is taken from the FDA biostatistical review.

Tables 6 and 7 summarize the results of the primary endpoint, efficacy failure, for each treatment group at 3 and 6 months, respectively. The following are included in the tables.

1. The overall rates of efficacy failure for each treatment group and the rates for each component of the composite endpoint.
2. 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 sirolimus tablet group than in the oral solution group.

The overall rate of efficacy failure at 3 months in the tablet treatment group (24.7%) is equivalent to that in the oral solution treatment group (23.5%). The upper bound of the 95% confidence interval for the difference in rates is less than 10%.

Table 6
Efficacy Failure at 3 months¹

	Sirolimus Oral Solution (n=238)	Sirolimus Tablet (n=239)
Overall rate of efficacy failure, n(%)	56 (23.5)	59 (24.7)
Acute rejection	45 (18.9)	42 (17.6)
Graft loss	8 (3.4)	15 (6.3)
Death	3 (1.3)	2 (0.8)
Stratified differences in rates (95% CI)		1.0 (-6.9, 8.9)

¹ FDA Statistical review.

Between 3 and 6 months, there were 6 additional efficacy failures in each treatment group. These included 5 acute rejections and 1 death in the oral solution treatment group and 4 acute rejections and 2 deaths in the tablet treatment group. Thus, the overall rates of efficacy failure at 6 months increased to 27.2% in the tablet treatment group and 26.1% in the oral solution treatment group. The upper bound of the 95% confidence interval for the difference in rates is less than 10%, which implies equivalence of the two sirolimus formulations.

Table 7
Efficacy Failure at 6 months¹

	Sirolimus Oral Solution (n=238)	Sirolimus Tablet (n=239)
Efficacy failure at 6 months, n(%)	62 (26.1)	65 (27.2)
Components of efficacy failure:		
Acute rejection	50 (21.0)	46 (19.2)
Graft loss	8 (3.4)	15 (6.3)
Death	4 (1.7)	4 (1.7)
Stratified differences in rates (95% CI)		1.1 (-7.0, 9.2)

¹ FDA Statistical review

Reviewer's note: *The protocol defined an endpoint at 3 months. The Applicant was requested to perform an analysis at 6 months because this endpoint had been used to support the activity of sirolimus in the original NDA. There are relatively few additional failures at 6 months compared to 3 months. The conclusions drawn at 6 months are similar to those reported by the sponsor for efficacy failure at 3 months.*

This is a composite endpoint and most of the rejection is due to lower grades of rejection (grades I and II). The rate of efficacy failure for the tablet minus the rate of efficacy failure for the solution is a value in favor of the oral solution. However, the overall rates of efficacy failure were still close to what would be expected with such a regimen. The difference between the oral solution group and the tablet group was small and the 95% confidence interval for this difference was narrow enough to

reliably exclude an unacceptable difference in efficacy—although, this is difficult to quantitate when using a composite endpoint.

Table 8 includes the results of patient and graft survival 12 months after transplantation for each treatment group. Differences between sirolimus oral solution and tablet were assessed using Fisher's exact test. There was not a statistically significant difference in the rate of patient and graft survival between the two sirolimus formulations. The Rapamune® oral solution treatment group had a slightly better patient and graft survival rate at 12 months than the tablet treatment group. The exact 95% confidence interval about the difference in patient and graft survival rates indicates equivalence at a delta less than 15%. The lower bound of this confidence interval is -10.2. The upper bound of the confidence interval for relative risk implies 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 sirolimus tablet compared to the oral solution. Patients who died with a functioning graft accounted for less than 35% of the total graft losses. There were numerically more pure graft losses in patients who received the tablet formulation than in patients who received the oral solution.

Table 8
Patient and Graft Survival at 12 months¹

	Sirolimus Oral Solution (n=238)	Sirolimus Tablet (n=239)
Patient and Graft survival, n(%)	219 (92.0)	212 (88.7)
Graft loss	11	20
Death w/ functioning graft	8	7
Fisher's exact p-value		0.278
Relative risk (95% CI)		1.42 (0.81, 2.47)
Differences in rates (Exact 95% CI)		-3.3 (-10.2, 2.8)

¹FDA Statistical review

Reviewer's note: Patient and graft survival at 12 months is an endpoint of interest because it is believed to predict long-term outcome. There is a numerical difference in graft loss which appears unfavorable to the tablet formulation. There is little difference with respect to death with a functioning graft or patient survival. Overall, the patient survival at 12 months is excellent and the 95% confidence interval of the difference is narrow enough to exclude with reasonable certainty the possibility of an unacceptable decrease in patient (or graft) survival at 12 months.

Table 9 includes the results of patient survival 12 months after transplantation for each treatment group. There was not a statistically significant difference in the rate of patient survival between sirolimus formulations. The exact 95% confidence interval about the difference in survival rates indicates equivalence at a delta less than 5%.

Table 9
Patient Survival at 12 months¹

	Sirolimus Oral Solution (n=238)	Sirolimus Tablet (n=239)
Patient survival, n(%)	228 (95.8)	230 (96.2)
Death	10	9
Fisher's exact p-value		0.271
Relative risk (95% CI)		0.90 (0.37, 2.17)
Differences in rates (Exact 95% CI)		0.4 (-4.4, 5.4)

¹ FDA Statistical review

The first acute rejection episode was classified by the [] criteria of grade I (mild), grade II (moderate), or grade III (severe) acute rejection. The distribution of histological grade of acute rejection was not significantly different between the oral solution and tablet treatment groups. Most of the rejection was grade I and grade II rejection.

Rates of efficacy failure were also 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. In addition, the effect of the treatment groups on the rate of efficacy failure is assessed by controlling for each of these stratification variables. (see Table 10).

Table 10
Efficacy Failure at 6 months
Selected subgroups¹

Subgroup	Sirolimus Oral Solution (n=238)	Sirolimus Tablet (n=239)	Stratified Difference (95% CI)
Recipient Race			1.0 (-7.3, 9.3)
Black	18/54 (33.3)	18/59 (30.5)	
Non-black	44/184 (23.9)	47/180 (26.1)	
Recipient Gender			1.2 (-7.1, 9.6)
Female	30/95 (31.6)	27/93 (29.0)	
Male	32/143 (22.4)	38/146 (26.0)	
Donor Source			0.9 (-7.5, 9.3)
Cadaver	47/158 (29.8)	46/170 (27.1)	
Living	15/80 (18.8)	19/69 (27.5)	
Related	8/55 (14.6)	12/49 (24.5)	
Unrelated	7/25 (28.0)	7/20 (35.0)	
Number of HLA mismatches			0.8 (-7.5, 9.1)
0 to 2	8/62 (12.9)	12/55 (21.8)	
3 to 6	54/176 (30.7)	53/184 (28.8)	

¹ FDA Statistical review

The confidence intervals stratified by recipient race, recipient gender, donor source, or number of HLA mismatches are all similar to the confidence interval calculated for the primary analysis of efficacy failure. Thus, the robustness of the results of the primary analysis is supported by these subgroup analyses.

There were no statistically significant differences between the treatment groups for any of the subgroups. The rate of efficacy failure is numerically greater for black patients than non-black patients. Female patients have numerically greater efficacy failure rates than male patients with both sirolimus formulations. The efficacy failure rates are similar for patients who receive a cadaveric or living donor organ with the exception of patients who receive a living donor organ on sirolimus oral solution. Though, not statistically different, these patients have a numerically lower efficacy failure rate. The low number of failures seen by patients receiving living related donor organs causes this numeric difference.

Reviewer's note: *At this time, it is difficult to speculate about why the efficacy failure rate would be higher in living related renal transplant patients receiving sirolimus tablet (24.5%) when compared with living related renal transplant patients receiving sirolimus solution (14.6%).*

Patients with 3 to 6 HLA mismatches have higher efficacy failure rates than patients with 0 to 2 HLA mismatches. Patients with 0 to 2 HLA mismatches and treated with sirolimus oral solution have a numerically smaller efficacy failure rate than those patients treated with the tablet.

There was also no statistically significant difference between treatment groups in the time to efficacy failure within the first 6 months after transplantation.

Efficacy Conclusions

1. Rapamune® oral solution and tablet formulations demonstrated, at the dose of 2 mg/day, comparable rates of efficacy failure at 3 and 6 months post transplantation, defined as first occurrence of biopsy-proven acute rejection, graft loss, or death.
2. Rapamune® oral solution and tablet formulations demonstrated, at the dose of 2 mg/day, comparable patient and graft survival at 12 months post-transplantation.
3. Overall, when used at doses of 2 mg/day with cyclosporine and corticosteroids, Rapamune® tablet is as effective as Rapamune® oral solution, in preventing graft rejection in renal transplant recipients.
4. The relative efficacy of Rapamune® tablet, compared to Rapamune® oral solution, has not been evaluated at doses higher than 2 mg per day.

9.0 Safety Evaluation

Of the 477 patients enrolled in this study, 457 patients received at least 1 dose of sirolimus; 228 received the liquid formulation and 229 received the tablet.

Exposure

The majority of patients received total daily doses of > 1 mg to 2 mg, which approximates the dose of sirolimus intended for the study (2 mg/day). These results indicate that patients enrolled in both sirolimus treatment groups were adequately exposed to potentially therapeutic doses of study drug.

Of the patients who received sirolimus therapy for up to 90 days (3 months), 183 received the solution and 195 received the tablet. Of those who received sirolimus therapy up to 194 days (6 months), 156 received the solution and 166 received the tablet.

Reviewer's note: In addition to sirolimus the immunosuppressive regimen included cyclosporine and corticosteroids. Cyclosporine trough levels were similar across treatment groups. Steroid use, however, was greater for the sirolimus solution patients in the post-study period. Please see the Biopharmaceutics review for additional details.

Dose Reduction

Dose reductions of study medication were permitted by the protocol to palliate toxic effects that the investigators considered to be possibly related to sirolimus. The percentages of patients who had no dose reduction, a temporary dose reduction, or a permanent dose reduction, and whose last recorded study medication day was before day 166, were similar for both the solution and the tablet treatment groups. The percentages of the same categories for patients whose last recorded study medication day was on or after day 166 were also similar for the solution and tablet groups. Note that this analysis is based on a snapshot of the data at 6 months. Patients continuing on study drug may move to different categories depending upon their subsequent dosing. The percentage of patients who did not require any permanent or temporary dose reduction while receiving sirolimus was 44.5% in the oral solution group and 50.2% in the tablet group. These values are similar to each other and to the overall rate observed of 44.8% in the pivotal phase III studies (NDA 21-083, studies 301 and 302).

Adverse Events

Most adverse events occurred in the first six months post-transplant. Additional safety information on cumulative adverse events post-transplant was submitted in the 4 month safety update report (dated February 29, 2000). No new patterns of adverse events were detected in the safety update. Adverse events were recorded at the time of discontinuation of sirolimus therapy, through 1 month after discontinuation of sirolimus use. Limited

adverse event recording (including infections and malignancies) were to occur at 3, 6, and 12 months after transplantation. Patient and graft survival were evaluated at the time of discontinuation of sirolimus therapy and at 3, 6, and 12 months after transplantation. Adverse events were coded according to the COSTART system using the preferred term and body system.

Reviewer's note: *Because the AUC of the sirolimus tablet is expected to be higher than the AUC in those receiving the sirolimus oral solution, it is important to examine whether adverse events known to be associated with sirolimus were increased in the group receiving the tablet compared to those receiving the solution.*

Table 11 depicts treatment emergent adverse events (TEAEs) that occurred with a frequency of greater than or equal to 20%. One or more treatment emergent adverse events that were not related to infection or malignancy were reported by 228 (99.6%) oral solution patients and 227 (99.6%) sirolimus tablet patients. The most commonly occurring TEAEs (reported in at least 20% of patients in any one treatment group) and the accompanying p-values are summarized by treatment group in Table 11. Acne was the only TEAE reported at a significantly higher ($p=0.035$) rate in the sirolimus oral solution group. The incidence of tremor was numerically higher in the sirolimus tablet arm (18.8% vs 26.3% $p=0.058$) but the incidence was lower than that reported in the Phase III trials for sirolimus oral solution NDA 21-083 (30-31%).

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Table 11Number (%) of Patients Reporting Treatment Emergent Adverse Events ($\geq 20\%$)¹

Body system Event	Sirolimus Oral Solution (n=229)	Sirolimus Tablet (n=228)	p-value
Any adverse experience (1 or more)	228 (99.6)	227 (99.6)	1.00
Body as a whole			
Abdominal pain	55 (24.0)	60 (26.3)	0.591
Asthenia	60 (26.2)	52 (22.8)	0.447
Back Pain	41 (17.9)	51 (22.4)	0.245
Fever	77 (33.6)	65 (28.5)	0.266
Headache	62 (27.1)	56 (24.6)	0.593
Pain	45 (19.7)	58 (25.4)	0.147
Cardiovascular system			
Hypertension	107 (46.7)	106 (46.5)	1.00
Digestive system			
Constipation	50 (21.8)	64 (28.1)	0.131
Diarrhea	72 (31.4)	78 (34.2)	0.551
Nausea	66 (28.8)	60 (26.3)	0.601
Vomiting	63 (27.5)	56 (24.6)	0.523
Hemic and lymphatic system			
Anemia	69 (30.1)	65 (28.5)	0.758
Metabolic and nutritional			
Creatinine increased	76 (33.2)	73 (32.0)	0.842
Edema	46 (20.1)	44 (19.3)	0.906
Hypercholesteremia	83 (36.2)	82 (36.0)	1.00
Hyperlipemia	95 (41.5)	103 (45.2)	0.451
Peripheral edema	151 (65.9)	149 (65.4)	0.922
Musculoskeletal system			
Arthralgia	48 (21.0)	52 (22.8)	0.652
Nervous system			
Tremor	43 (18.8)	60 (26.3)	0.058
Respiratory system			
Dyspnea	48 (21.0)	48 (21.1)	1.00
Skin and appendages			
Acne	63 (27.5)	43 (18.9)	0.035*
Study event associated with miscellaneous factors			
Local reaction to procedure	88 (38.4)	80 (35.1)	0.497

1. Table is taken from Applicant's 4 month safety update 2/29/00.

Reviewer's note: The rates of hyperlipidemia, hypercholesterolemia, elevated creatinine and anemia were similar across treatment groups.

Recently, there have been reports both submitted to FDA and reported in the medical literature of renal transplant recipients who developed interstitial pneumonitis, of a non-infectious etiology, while taking Rapamune® as part of their immunosuppressive regimen. Several patients improved with discontinuation of Rapamune® raising concerns that Rapamune® may cause a drug-induced interstitial pneumonitis. Consequently, the Applicant has submitted a change to the label that will alert health care providers regarding this new adverse event. During this NDA review, adverse events related to the respiratory system were given particular attention.

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Sirolimus liquid had 21 cases of pneumonia at 6 months. Thirteen of the 21 cases had organisms identified, although only 7 of the 13 cases had organisms that were typical pulmonary pathogens. Median time to presentation was 42 days and the mean time of presentation was 61.3± SEM 12.6 days. Sirolimus tablet had 15 cases of pneumonia and 5 had infectious organisms specified and 10 cases did not have organisms specified. Median time to event was 63 days. Diagnosis could be confirmed by "any method" which could be sputum culture, chest x-ray, clinical suspicion. None of these cases appeared to fit an interstitial pneumonitis type of presentation.

Rates of dyspnea in study 309 were 21% in each sirolimus arm. The rates of dyspnea in the original NDA 21-083 (study 301 and study 302) for sirolimus oral solution were 22-24% for the 2 mg dose and 28-30% for the 5 mg sirolimus dose. Rates of dyspnea were 23% for the azathioprine control in study 301 and 30% for the placebo control in study 302. Thus, no significant differences were noted across treatment arms or studies.

Rates of "upper respiratory infection" were 20-26% for the 2 mg dose and 23-24% for the 5 mg sirolimus doses respectively and 13% for the azathioprine control and 23% for the placebo control in the original NDA21-083. Once again, no significant differences were noted across treatment arms or studies .

No cases suggestive of pneumonitis were reported as deaths or discontinuations but the Applicant is currently reviewing its data base for both this current sirolimus tablet NDA (21-110) and the original sirolimus oral solution NDA (21-083) to assess for cases of bronchiolitis obliterans obstructing pneumonia (BOOP), interstitial pneumonitis or fibrosis.

Table 12 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 sirolimus trials.

**APPEARS THIS WAY
ON ORIGINAL**

Table 12

Number (%) of Patients Reporting Clinically Important TEAE
Excluding Infection and Malignancy¹

Body system Event	Sirolimus Oral Solution (n=229)	Sirolimus Tablet (n=228)	p-value
Body as a whole			
Lymphocele	39 (17.0)	28 (12.3)	0.186
Cardiovascular system			
Myocardial infarction	1 (0.4)	4 (1.8)	0.216
Tachycardia	26 (11.4)	26 (11.4)	1.00
Digestive system			
Liver function tests abnormal	14 (6.1)	24 (10.5)	0.093
Pancreatitis	1 (0.4)	2 (0.9)	0.623
Endocrine system			
Diabetes mellitus	14 (6.1)	25 (11.0)	0.068
Hemic and lymphatic system			
Anemia	69 (30.1)	65 (28.5)	0.758
Leukopenia	18 (7.9)	21 (9.2)	0.620
Thrombocytopenia	32 (14.0)	40 (17.5)	0.307
Thrombotic thrombocytopenia purpura (TTP)	5 (2.2)	2 (0.9)	0.450
Metabolic and nutritional			
Hyperkalemia	43 (18.8)	31 (13.6)	0.162
Hypokalemia	28 (12.2)	22 (14.5)	0.495
Musculoskeletal system			
Arthralgia	48 (21.0)	52 (22.8)	0.652
Nervous system			
Hypertonia	15 (6.6)	5 (2.2)	0.037*
Respiratory system			
Epistaxis	5 (2.2)	10 (4.4)	0.202

1. Table is taken from Applicant's 4 month safety update 2/29/00.

The only clinically important TEAE that occurred more frequently in one of the two sirolimus treatment groups was hypertonia. Hypertonia occurred more frequently in the sirolimus oral solution group when compared to the sirolimus tablet group.

Reviewer's note: The rate of hematologic adverse events was similar across treatment groups in study 309 and similar to the rates of thrombocytopenia, leukopenia, anemia and TTP noted in the 2 mg sirolimus solution arm in NDA 21-083.

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Discontinuations for Adverse Events

Table 13 Discontinuations due to laboratory abnormalities¹

Laboratory Abnormalities	SRL solution (n=229)	SRL solution (n=228)	Total (n=457)
Anemia	1	2	3
Creatinine increased	3	4	7
Hypercholesterolemia	1	0	1
Hyperlipemia	3	1	4
Idiopathic thrombocytopenic purpura (ITP)	1	0	1
Leukopenia	2	0	2
Elevated liver function tests	1	1	2
Overdose/cyclosporine toxicity	2	1	3
Thrombocytopenia	2	4	6
Total	16	13	29

1. Table is taken from Applicant's 4 month safety update 2/29/00.

Reviewer's note: *Elevated creatinine levels, thrombocytopenia, and hyperlipemia were the most common laboratory abnormalities that led to patients discontinuing the study medication (see Table 13). Seventy-nine patients had sirolimus discontinued for adverse events other than infection and laboratory abnormalities. There were no significant differences in the number of these discontinuations between the treatment groups.*

In the original sirolimus solution NDA (21-083), some adverse events known to be associated with cyclosporine, such as tremor, were shown to be more common in the sirolimus treatment arm than in the control groups (azathioprine or placebo). It became of interest to examine whether the frequency of certain adverse events differed between patients who received sirolimus tablet and sirolimus solution within ethnic groups. Please keep in mind that the numbers of patients receiving Rapamune® tablet and solution in "non-white" ethnic groups were comparable but small, ranging from 8 to 55 patients. The following adverse event profiles were noted. Hyperglycemia was seen more frequently in Hispanic patients receiving Rapamune® tablet when compared to Hispanic patients receiving Rapamune® oral solution. Acne occurred more frequently in Black patients receiving Rapamune® oral solution when compared to Black patients receiving Rapamune® tablet. Hyperkalemia was seen more frequently in white patients receiving Rapamune® oral solution when compared to white patients receiving Rapamune® oral solution. Tremor occurred more frequently in Black patients receiving Rapamune® tablet (21.8%) when compared to Black patients receiving the oral solution (5.7%). However, the incidence of tremor in Black patients receiving Rapamune® oral solution (5.7%) was much lower than the incidence of tremor seen in white (21.8%), Asian (25%) and Hispanic (33.3%) patients who received Rapamune® oral solution in study 309. Nevertheless, after discussion

within the Division, the team leader believed that this difference in tremor across treatment groups for Black patients should be included in the label.

The mean cyclosporine and sirolimus trough levels were reported to be similar across treatment groups. Consequently, at this time, it is not possible to draw conclusions regarding whether these side effects were related to individually higher levels of sirolimus and/or elevated cyclosporine trough levels. Overall, the rate of premature discontinuation from study drug, because of adverse events was comparable across treatment groups.

Deaths, Graft loss and Malignancy

Deaths

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 through the data cutoff date (July 30, 1999) used for the 4 month safety update are summarized in Table 14.

Table 14
Summary of Deaths, Graft Loss, Malignancy, and Life-Threatening Adverse Events¹

Event	Sirolimus Oral Solution (n=238)	Sirolimus Tablet (n=239)
Death	10 (4.2)	9 (3.8)
Graft Loss (pure)*	11 (4.6)	20 (8.4)
Malignancy	6 (2.5)	9 (3.8)
Life-Threatening Adverse Event	20 (8.4)	16 (6.7)

1. FDA statistical review.

*Excludes death with a functioning graft

Nineteen patients died as of the study data cut-off date. Seventeen patients died after receiving at least one dose of sirolimus and 2 died after they were randomized into the study but before they received any study drug. There was no significant difference in the incidence of death in the oral solution group compared to the tablet group. In the investigators' opinion, one patient death in the oral solution group was thought to be probably related to the study medication. Five patient deaths were thought to possibly be related to the study medication (2 in the oral solution and 3 in the tablet). In both treatment groups, the most common causes of death were infections and cardiovascular events (see Table 15 below).

Table 15 Cause of Death at 12 months

Cause of Death at 0-12 months	SRL oral solution (n= 228)	SRL tablet (n= 229)
Vascular	5	3
Infection	4*	6
Malignancy	0	0
Other	1	0
Total	10	9

*One patient also had PTLD at autopsy.

Reviewer's note: Examination of the listings of cause of death and of the case report forms of the patients who died during the first 12 months did not reveal any unusual pattern across treatment groups. The leading causes of death were infection or vascular events. There was no statistically significant difference in the rate of patient survival between sirolimus formulations. Patient survival at 12 months was 95.8% for sirolimus oral solution and 96.2% for sirolimus tablet.

Pure Graft Loss

Table 16 includes the results of patient and graft survival 12 months after transplantation for each treatment group. Differences between sirolimus oral solution and tablet were assessed using Fisher's exact test. There was not a statistically significant difference in the rate of patient and graft survival between the two sirolimus formulations. The Rapamune[®] oral solution treatment group had a slightly better patient and graft survival rate at 12 months than the tablet treatment group

Table 16
Patient and Graft Survival at 12 months¹

	Sirolimus Oral Solution (n=238)	Sirolimus Tablet (n=239)
Patient and Graft survival, n(%)	219 (92.0)	212 (88.7)
Pure Graft loss	11	20
Death w/ functioning graft	8	7
Fisher's exact p-value		0.278
Relative risk (95% CI)		1.42 (0.85, 2.47)
Differences in rates (Exact 95% CI)		-3.3 (-10.2, 2.8)

1. FDA statistical review.

There were numerically more pure graft losses (excludes death with a functioning graft) in patients who received the tablet formulation than in patients who received the oral solution. See Table 17 which outlines the etiologies of graft loss.

Reviewer's note: In the sirolimus tablet group, 6 of the 20 patients experiencing pure graft loss did so because of ATN at ≤ 8 days. There were also no major differences in cold ischemia time across treatment groups that would account for the numerical differences in graft loss. Two of the graft losses in the tablet arm were second transplants and one graft loss in the tablet arm was a third transplant.

Overall, after reviewing the individual case report forms, I do not believe that drug failure accounted for the numerical differences in pure graft loss between sirolimus tablet and solution.

Table 17 Primary Etiology of Graft Loss¹

Etiology of Graft Loss	SRL solution (n=238)	SRL tablet (n=239)	Total (n=477)	p-value
Death with functioning graft	8(3.4)	7 (2.9)	15 (3.1)	0.80
Acute Tubular Necrosis (ATN)	2 (0.84)	7 (2.9)	9 (1.9)	0.176
Acute rejection	3 (1.3)	5 (2.1)	8 (1.7)	0.724
Renal vein or artery thrombosis	1 (0.4)	2 (0.8)	3 (0.6)	1.00
Thrombotic microangiopathy	1 (0.4)	0	1 (0.2)	0.499
Proliferative Arteriopathy (Infarction)	1 (0.4)	0	1 (0.2)	0.499
Prolonged Hypotension (Infarction)	0	1 (0.4)	1 (0.2)	1.00
Donor vascular Disease	0	1 (0.4)	1 (0.2)	1.00
Other	3 (1.3)	4 (2.2)	7 (1.5)	1.00
Total, without deaths	11(4.6)	20 (8.4)	31 (6.5)	0.136
Total, with deaths	20 (8.4)	28 (11.7)	46 (9.6)	0.278

1. Applicant analysis in 4 month safety update 2/29/00.

Malignancy and PTLD

There were 15 patients who had histologically confirmed malignancy:

-9 of these patients were in the sirolimus tablet arm with 6 patients having skin carcinoma, 1 case of melanoma, 1 patient had PTLD and 1 patient had large B cell non-Hodgkin's lymphoma

-6 patients were in the sirolimus oral solution arm with 4 having skin carcinoma, 1 patient with PTLD and 1 patient had a B-cell small lymphocyte lymphoma in the donor kidney.

Reviewer's note: The rates of PTLD in this trial are similar to that reported in the Phase III trials of sirolimus oral solution and other trials of immunosuppressive agents. The incidence of lymphoreticular and other malignancies were similar across

treatment groups. Despite the use of antilymphocyte antibody preparations for ATN, there was no evidence of an increased incidence of PTLD in either treatment arm.

Infection

12 month incidence rates (per 100 patients) for select clinically important infections are outlined in Table 18 below.

Table 18 Incidence of Infection at 12 months¹

Type of Infection	SRL solution N=238 Rate, n(%) Confidence Interval CI	SRL tablet N=239 Rate, n(%) Confidence Interval CI	Fisher's exact p-Value
Sepsis	13 (5.5) CI (2.94-9.16)	19 (8.0) CI (4.85-12.14)	0.36
CMV(generalized)	5 (2.1) CI (.69-4.83)	6 (2.5) CI (0.93-5.38)	1.000
CMV(tissue-invasive)	2 (0.8) CI 0.10-3.00	2 (0.8) CI (0.10-2.99)	1.000
Pneumonia	27 (11.3) CI (7.61-16.08)	21 (8.8) CI (5.52-13.12)	0.366
PCP pneumonia	0(0) CI (0-1.54)	1 (0.4) CI (0.01-2.31)	1.000
Herpes simplex	12 (5.0) CI (2.63-8.64)	12 (5.0) CI (2.62-8.61)	1.000
Herpes zoster	5 (2.1) CI (0.69-4.83)	10 (4.2) CI (2.02-7.56)	0.294
UTI/Pyelonephritis	54 (22.7) CI (17.53-28.54)	61 (25.5) CI (20.12-31.54)	0.521
Wound infection	36(15.1) CI (10.82-20.32)	27(11.3) CI (7.58-16.01)	0.227
Epstein-Barr virus	0(0) CI (0-1.54)	1 (0.4) CI (0.01-2.31)	1.000

1.From Applicant's 4 month safety update.

Reviewer's note: *There were no significant differences in the rates of infection in patients assigned to the sirolimus tablet or solution groups. Patients were mandated to take PCP prophylaxis for the first 12 months post-transplant and CMV prophylaxis was encouraged for CMV negative recipients of CMV seropositive donor organs or during periods of heightened immunosuppression.*

Hyperlipidemia

The Applicant reports the incidence of hypercholesterolemia was 5.2% in the patients receiving Rapamune® solution and 36% in the patients receiving Rapamune® tablet. This lipid analysis evaluated a cohort of patients who had normal cholesterol and triglycerides at study onset and developed hyperlipidemia while on study drug. Hyperlipidemia has been identified as a major side-effect of sirolimus.

Reviewer's note: The numbers of patients with the development of elevated cholesterol or triglyceride values on therapy was similar across treatment groups. The use of lipid-lowering agents was also similar across treatment groups.

The percentage of patients who began study 309 with normal (<200 mg/dl) serum cholesterol and developed elevated cholesterol i.e. ≥ 240 mg/dl was 18.5% (17/92 patients) in the Rapamune® solution arm and 25% (23/92 patients) in the Rapamune® tablet arm.

The percentage of patients who began study 309 with normal triglycerides (<200 mg/dl) and developed elevated triglycerides (≥ 500 mg/dl) on therapy was 2.1% (2/94 patients) in the Rapamune® solution arm and 3.1% (3/96 patients) in the Rapamune® tablet arm.

Liver Function Test elevations

There was no difference in the mean values for LDH, or serum aminotransferase (AST/ALT) values between the two treatment groups. Bilirubin values were not mandated for collection in this protocol. Liver function tests were abnormal in 6.1% of patients receiving Rapamune® oral solution and 10.5% of patients receiving Rapamune® tablet.

Reviewer's note: Elevated liver function tests were not found to be major adverse events in the original NDA 21-083.

Hematologic Parameters

There were no significant differences between treatment arms for hemoglobin values, WBC counts or platelet counts at months 1, 3, 6, 9 or 12.

Hemoglobin

Adjusted mean values for hemoglobin were not significantly different between sirolimus formulations. The incidence of anemia was 28.5-30.1% in study 309.

Reviewer's note: In NDA 21-083, the incidence of anemia was 23-27% for the sirolimus 2 mg and 33-37 % for the 5 mg arms in studies 301 and 302.

WBC

Regarding the development of leukopenia, there were no significant differences between treatment groups in this study. Adjusted mean values for WBC ($10^9/L$) were within normal limits at 12 months. The incidence of leukopenia was 7.9% for the sirolimus solution and 9.2 % for the sirolimus tablet.

Reviewer's note: In NDA 21-083, the incidence of leukopenia was 9-15% for the sirolimus 2 mg and 5 mg arms in studies 301 and 302.

Platelets

There was no difference in the adjusted mean values for the solution and tablet at months 1, 3, or 6 in platelet counts. No patients had grade 3 ($< 50 \times 10^9/L$) reductions in platelet counts in either treatment group. At month 1, $< 4\%$ of patients in either treatment group had counts $< 100 \times 10^9/L$. The incidence of thrombocytopenia in this study was 14% for the sirolimus oral solution and 17.5% for the sirolimus tablet.

Reviewer's note: The incidence of thrombocytopenia was 13-20% in NDA 21-083 for sirolimus 2 mg and 5 mg doses.

TTP

The incidence of TTP was similar across treatment arms in this study with Rapamune solution having an incidence of 2.2 % and Rapamune tablet having an incidence of 0.9%.

Reviewer's note: The incidence of TTP in NDA 21-083 ranged from 1-9% for the 2 mg and 5 mg sirolimus treatment arms.

GFR

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. An 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 22% 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.

Table 19 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 are not significantly different for the sirolimus oral solution compared to the tablet formulation.

Table 19

Mean (sd) GFR and Serum Creatinine at 12 Months¹

	Sirolimus Oral Solution	Sirolimus Tablet	<u>P-</u> <u>value</u>
GFR (cc/min)	58.3 (21.1) n=166	58.5 (18.3) n=162	0.9102
Serum Creatinine (mg/dL)	1.91 (0.98) n=165	1.86 (0.79) n=163	0.6161

1. FDA statistical review.

Reviewer's Note: GFR is assessed using the calculated 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. As in the original NDA 21-083, GFR continues to be less than 60 cc/min at 12 months.

Effects of race, sex and age

There were numerical differences across treatment arms for the sirolimus tablet vs the sirolimus oral solution when adverse events were stratified by sex, age and race.

Reviewer's note: Males and patients who were greater than 65 years old, who received sirolimus tablet, had an increased incidence of tremor when compared to males or those greater than 65 years old who received sirolimus oral solution. However, the overall number of patients in the age category of greater than 65 years was small. Tremor may be due to cyclosporine or Rapamune® and trough levels of both these drugs may need to be more closely monitored in patients who develop tremor.

Constipation was seen more frequently in 41 to 65 year olds receiving the tablet when compared with 41 to 65 year olds receiving the oral solution.

Please see p. 25 of this review for a discussion regarding the differences seen in adverse events that occurred within ethnic groups comparing patients treated with sirolimus oral solution and tablet.

Human Reproduction Data

There is no data at this time to support the use of sirolimus in pregnancy, however the Applicant has created a pregnancy registry.

10.0 Labeling Review

The proposed Package Insert, included in the original NDA submission, was revised after discussion between the FDA and the Applicant. The revision dated August 21, 2000 is the final version agreed upon, and it incorporates all of the successive changes requested by the FDA. Important changes included:

“After administration of Rapamune® Tablets and a high-fat meal in 24 healthy volunteers, C_{max} , t_{max} and AUC showed increases of 65%, 32% and 23% respectively. To minimize variability, both Rapamune® Oral Solution and Tablets should be taken consistently with or without food (SEE DOSAGE AND ADMINISTRATION).”

“2-mg Rapamune® oral solution has been demonstrated to be clinically equivalent to 2-mg Rapamune oral tablets; hence, are interchangeable. However, it is not known whether higher doses of Rapamune® oral solution are clinically equivalent to higher doses of the tablets on a mg to mg basis. (See Clinical Pharmacology: Absorption)”.

“Other clinical experience: Cases of pneumonitis with no identified infectious etiology, sometimes with an interstitial pattern, have occurred in patients receiving immunosuppressive regimens including Rapamune®. In some cases the pneumonitis has resolved upon discontinuation of Rapamune®.”

11.0 Reviewer's comments and conclusions

1. Although not bioequivalent, Study 309 has demonstrated that sirolimus oral solution and sirolimus tablet are clinically equivalent in the prevention of acute rejection at 3 and 6 months post-transplant. The rates of patient and graft survival at one year were equivalent.
2. Adverse events that continue to warrant monitoring include laboratory parameters such as anemia, thrombocytopenia, leukopenia, hyperlipidemia and elevated creatinine and decreased GFR. No new safety concerns were identified in this trial.
3. Although pneumonitis was not identified as a major adverse event in this study, case reports have now been reported both in the literature and to the FDA. Consequently, it will be important to monitor patients for the development of this entity. If no infectious etiology is identified as a cause for interstitial pneumonitis, consideration should be given to discontinuation of Rapamune® until further information and recommendations become available.
4. As in the original NDA 21-083, patients maintained on Rapamune® oral solution or Rapamune® tablet continue to sustain GFR's of less than 60 cc/min at 12 months.
5. Patients should not take sirolimus tablet with food as this may increase the C_{max} of the drug. If higher doses of the tablet are utilized, this may increase the risk for development of adverse events. It has not yet been established that higher doses of the sirolimus tablet are clinically equivalent to similar and higher doses of the oral solution.

6. Benefits of the tablet include convenience and room temperature stability which may enhance compliance.

12.0 Recommendations

Approval

The 2 mg/day dose of Rapamune® tablet should be approved for the prophylaxis of rejection in renal transplant recipients.

13.0 Phase IV Commitments

Clinical

1. Evaluate the optimal dose of sirolimus in renal transplant patients, who are at high risk for acute rejection, by conducting a well-controlled, comparative study or studies, to further define the optimal dose or concentration in this population. Patients from any or all of the following groups might be included:
 - Black patients
 - Patients with retransplants.
 - Patients with high panel-reactive antibodies.
 - Patients with greater than or equal to 4 human leukocyte antigen mismatches.
 - Patients with multiorgan transplants.
2. Conduct an appropriate study or studies to better define the type and duration of hyperlipidemia associated with the use of sirolimus. In particular, measure and analyze total fasting serum cholesterol and triglycerides, as well as high-density lipids/low-density lipids, and lipoprotein A. Transplant recipients with and without a lipid disorder prior to transplant will be included, and the use of lipid-lowering agents and other specific interventions will be evaluated.
3. As part of the continuing development of sirolimus, assess its effect on long-term renal function using GFR in patients receiving kidney or other solid organ transplants.
4. In ongoing and future studies of sirolimus, evaluate the impact of this drug on liver function tests in recipients of kidney or liver transplants who may have hepatitis B virus and/or hepatitis C virus infection.
5. Collect and report 1-year follow-up safety data from the ongoing Phase 3 study 309. Data pertaining to GFR and serum creatinine will be included as follow-up information and will be available in March 2001.
6. Collect long-term data from study 306 in which some patients have on the tablet for several years, which will be available in June 2001.

Clinical Pharmacology

7. Evaluate the optimum therapeutic concentration range for sirolimus and the value of reduced cyclosporine concentrations in combination with sirolimus. Employ therapeutic drug monitoring and logistic regression modeling in both high- and low-risk patients.
8. Conduct a study or studies to evaluate the effect of ethnicity on the pharmacokinetics of sirolimus so as to facilitate the determination of the optimum dosing regimen among other ethnic origins. Such a determination will be made using a population pharmacokinetics analysis, preferably using mixed effects modeling.

14. Financial Disclosure

There were no noticeable differences in efficacy or safety results among the clinical investigation sites.

Reviewer's note: Financial disclosure statements were submitted by investigators who participated in pivotal study 309. It was noted that Dr. Barry Kahan received [REDACTED] [REDACTED] from the Applicant. Dr. Kahan's site enrolled 32 of 477 study patients. A question was raised regarding potential investigator bias. However, after examination of the efficacy data, stratified by study site, no evidence of bias was detected.

**APPEARS THIS WAY
ON ORIGINAL**

/S/

8/18/00

Rosemary Tiernan, M.D.
Medical Officer, HFD-590

/S/

8/19/00

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CC:

- Archival NDA 21-110
- HFD-590/Division file
- HFD-590/DivDir/Albrecht
- HFD-590/MO-TL/Cavaillé-Coll
- HFD-590/RPM/Bacho
- HFD-590/Stat-TL/Higgins
- HFD-590/Stat/Dixon
- HFD-590/Chem-TL/Schmuff
- HFD-590/Chem/Seggel
- HFD-590/PT-TL/Hastings
- HFD-590/PT/Kunder
- HFD-590/Bph-TL/Ajayi
- HFD-590/Bph/Kumi
- HF-2/MedWatch (with labeling/labeling review)
- HFD-095/DDMS-IMT (with labeling)
- HFD-40/DDMAC (with labeling)
- HFD-613/OGD (with labeling)
- HFD-400/OPDRA (with labeling)
- HFD-102/Post Marketing PM
- HFD-830/DNDC Division Director/Chen
- HFI-20/Press Office (with labeling)
- HFD-104/Peds/V.Kao (with labeling)

Concurrence:

- HFD-590/DivDir/Albrecht
- HFD-590/MO-TL/Cavaillé-Coll

/S/ 8/25/00

/S/ 8/19/00