CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

Trade Name: **Rapamune**

Generic Name: **Sirolimus**

Sponsor: **Wyeth Ayerst Research**

Approval Date: **April 11, 2003**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-006
NDA 21-110/S-004

Wyeth Pharmaceuticals, Inc.
Attention: Randy Brenner
Manager, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Brenner:

Please refer to your supplemental new drug applications dated April 6 and 16, 2001, received April 9 and 18, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rapamune® (sirolimus) Oral Solution, 1 mg/mL, and Tablets, 1 and 2 mg.

We acknowledge receipt of your submissions dated:

February 15, 2002	January 22, 2003 (2)	January 31, 2003
February 12, 2003	February 21, 2003	March 14, 2003
March 24, 2003	March 27, 2003	March 31, 2003
April 2, 2003	April 3, 2003	

Your submission of October 11, 2002, constituted a complete response to our February 8, 2002 action letter.

These supplemental new drug applications provide for the use of Rapamune® (sirolimus) Oral Solution and Tablets within an immunosuppressive regimen that would allow for the withdrawal of cyclosporine 2 to 4 months after renal transplantation in patients considered at low to moderate immunologic risk for renal transplant rejection.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted April 3, 2003).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as they are available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 21-083/S-006 and 21-110/S-004." Approval of these submissions by FDA is not required before the labeling is used.

FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your products in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling.

Please submit three copies of the introductory promotional materials that you propose to use for this modification to the indication for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to each NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
4/11/03 09:41:38 AM
NDAs 21-083/S-006 & 21-110/S-004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-083/S-006
NDA 21-110/S-004

Wyeth-Ayerst Research
Attention: Randy Brenner
Manager, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Brenner:

Please refer to your supplemental new drug applications dated April 6 and 16, 2001, received April 9 and 18, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rapamune® (sirolimus) Oral Solution, 1 mg/mL, and Tablets, 1 mg.

We acknowledge receipt of your submissions dated:

April 25, 2001	August 8, 2001	January 8, 2002 (2)
January 11, 2002	January 22, 2002	

These supplemental new drug applications provide for the use of Rapamune® (sirolimus) Oral Solution and Tablets within an immunosuppressive regimen that would allow for the elimination of cyclosporine 2 to 4 months after renal transplantation.

We have completed the review of these applications as amended and they are approvable. Before the applications may be approved, however, it will be necessary for you to confirm the safety and efficacy of this regimen. This may be accomplished by providing the following information:

1. Conduct an intent-to-treat analysis of safety, acute rejection, patient and graft survival, and the change in renal function over time up to 24 months post-transplantation in Study 310, which would demonstrate sustained improvement in renal function after withdrawal of cyclosporine. This analysis should include measurement of renal function at 6, 12, 18 and 24 months post-transplantation, in all subjects randomized, whether or not they continued on study drug. It is recommended that such analyses include a slope intercept analysis of serum creatinine clearance over time.
2. Address the impact of lost patients including disproportionate discontinuation and dropout in the two arms of the studies on the conclusions that may be made regarding the safety of the two regimens.
3. Complete your postmarketing commitment to provide long-term information from studies 301 and 302, including intent-to-treat information on renal function, whether or not patients continued on study drug. The 24-month reports submitted for these studies have only included on-therapy analyses of renal function and therefore do not meet this postmarketing

commitment. Include a slope intercept analysis of serum creatinine clearance as well.

6. Define a therapeutic concentration range for sirolimus therapeutic drug monitoring in renal transplant patients whose cyclosporine has been eliminated by providing data and analyses that support this range and identifies the efficacious and maximum tolerated (safe) concentration.

If you are unable to provide all of the information requested above it would be necessary to conduct an additional adequate well-controlled trial of cyclosporine withdrawal and concentration-controlled sirolimus in U.S. renal transplant patients. This study should address the heterogeneity of U.S. renal transplant recipients. You may submit a written protocol for such a study to your IND for our review.

In addition, it will be necessary for you to submit draft labeling revised to reflect the additional information provided.

Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw these supplemental applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
2/8/02 03:48:21 PM
NDA 21-083/S-006 and NDA 21-110/S-004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

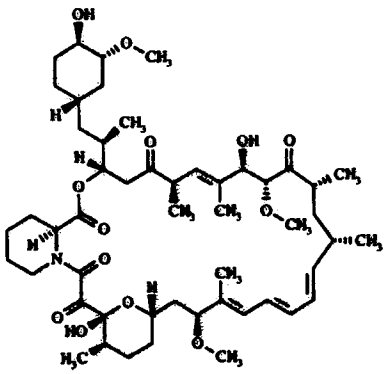
LABELING

Rapamune®
(sirolimus)
Oral Solution and Tablets

WARNING:
Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune®. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

Rapamune® (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34, 34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula of sirolimus is shown below.



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Rapamune® is available for administration as an oral solution containing 1 mg/mL sirolimus. Rapamune is also available as a white, triangular-shaped tablet containing 1-mg sirolimus, and as a yellow to beige triangular-shaped tablet containing 2-mg sirolimus.

The inactive ingredients in Rapamune® Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5% ethanol.

The inactive ingredients in Rapamune® Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, and other ingredients. The 2 mg dosage strength also contains iron oxide yellow 10 and iron oxide brown 70.

CLINICAL PHARMACOLOGY

Mechanism of Action

Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle.

Studies in experimental models show that sirolimus prolongs allograft (kidney, heart, skin, islet, small bowel, pancreatico-duodenal, and bone marrow) survival in mice, rats, pigs, and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and prolonged the graft survival in presensitized rats. In some studies, the immunosuppressive effect of sirolimus lasted up to 6 months after discontinuation of therapy. This tolerization effect is alloantigen specific.

In rodent models of autoimmune disease, sirolimus suppresses immune-mediated events associated with systemic lupus erythematosus, collagen-induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and autoimmune uveoretinitis.

Pharmacokinetics

Sirolimus pharmacokinetic activity has been determined following oral administration in healthy subjects, pediatric dialysis patients, hepatically-impaired patients, and renal transplant patients.

Absorption

Following administration of Rapamune® (sirolimus) Oral Solution, sirolimus is rapidly absorbed, with a mean time-to-peak concentration (t_{max}) of approximately 1 hour after a single dose in healthy subjects and approximately 2 hours after multiple oral doses in renal transplant recipients. The systemic availability of sirolimus was estimated to be approximately 14% after the administration of Rapamune Oral Solution. The mean bioavailability of sirolimus after administration of the tablet is about 27% higher relative to the oral solution. Sirolimus oral tablets are not bioequivalent to the oral solution; however, clinical equivalence has been demonstrated at the 2-mg dose level. (See **Clinical Studies** and **DOSAGE AND ADMINISTRATION**). Sirolimus concentrations, following the administration of Rapamune Oral Solution to stable renal transplant patients, are dose proportional between 3 and 12 mg/m^2.

Food effects: In 22 healthy volunteers receiving Rapamune Oral Solution, a high-fat meal (861.8 kcal, 54.9% kcal from fat) altered the bioavailability characteristics of sirolimus. Compared with fasting, a 34% decrease in the peak blood sirolimus concentration (C_{max}), a 3.5-fold increase in the time-to-peak concentration (t_{max}), and a 35% increase in total exposure (AUC) was observed. 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**).

Distribution

The mean (± SD) blood-to-plasma ratio of sirolimus was 36 ± 17.9 in stable renal allograft recipients, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (V_{ss}/F) of sirolimus is 12 ± 7.52 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins. In man, the binding of sirolimus was shown mainly to be associated with serum albumin (97%), α_1-acid glycoprotein, and lipoproteins.

Metabolism

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7) major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Glucuronide and sulfate conjugates are not present in any of the biologic matrices. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

Excretion

After a single dose of [^{14}C]sirolimus in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine.

Pharmacokinetics in renal transplant patients

Rapamune Oral Solution: Pharmacokinetic parameters for sirolimus oral solution given daily in combination with cyclosporine and corticosteroids in renal transplant patients are summarized below based on data collected at months 1, 3, and 6 after transplantation (Studies 1 and 2; see **CLINICAL STUDIES**). There were no significant differences in any of these parameters with respect to treatment group or month.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS (MULTIPLE DOSE ORAL SOLUTION)[a,b]

N	Dose	$C_{max,ss}$[c] (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$[c] (ng•h/mL)	CL/F/WT[d] (mL/h/kg)
19	2 mg	12.2 ± 6.2	3.01 ± 2.40	158 ± 70	182 ± 72
23	5 mg	37.4 ± 21	1.84 ± 1.30	396 ± 193	221 ± 143

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).
b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).
c: These parameters were dose normalized prior to the statistical comparison.
d: CL/F/WT = oral dose clearance.

Whole blood sirolimus trough concentrations (mean ± SD), as measured by immunoassay, for the 2 mg/day and 5 mg/day dose groups were 8.6 ± 4.0 ng/mL (n = 226) and 17.3 ± 7.4 ng/mL (n = 219), respectively. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated ($r^2 = 0.96$) with $AUC_{\tau,ss}$. Upon repeated twice daily administration without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimus increases approximately 2 to 3-fold over the initial 6 days of therapy at which time steady state is reached. A loading dose of 3 times the maintenance dose will provide near steady-state concentrations within 1 day in most patients. The mean ± SD terminal elimination half life ($t_{½}$) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

Rapamune Tablets: Pharmacokinetic parameters for sirolimus tablets administered daily in combination with cyclosporine and corticosteroids in renal transplant patients are summarized below based on data collected at months 1 and 3 after transplantation (Study 3; see **CLINICAL STUDIES**).

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS (MULTIPLE DOSE TABLETS)[a,b]

n	Dose (2 mg/day)	$C_{max,ss}$[c] (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$[c] (ng•h/mL)	CL/F/WT[d] (mL/h/kg)
17	Oral solution	14.4 ± 5.3	2.12 ± 0.84	194 ± 78	173 ± 50
13	Tablets	15.0 ± 4.9	3.46 ± 2.40	230 ± 67	139 ± 63

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).
b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).
c: These parameters were dose normalized prior to the statistical comparison.
d: CL/F/WT = oral dose clearance.

Whole blood sirolimus trough concentrations (mean ± SD), as measured by immunoassay, for 2 mg of oral solution and 2 mg of tablets over 6 months, were 8.9 ± 4.4 ng/mL (n = 172) and 9.5 ± 3.9 ng/mL (n = 179), respectively. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated ($r^2 = 0.85$) with $AUC_{\tau,ss}$. Mean whole blood sirolimus trough concentrations in 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.

Average Rapamune doses and sirolimus whole blood trough concentrations for tablets administered daily in combination with cyclosporine and following cyclosporine withdrawal, in combination with corticosteroids in renal transplant patients (Study 4; see **CLINICAL STUDIES**) are summarized in the table below.

AVERAGE RAPAMUNE DOSES AND SIROLIMUS TROUGH CONCENTRATIONS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS AFTER MULTIPLE DOSE TABLET ADMINISTRATION

	Rapamune with Cyclosporine Therapy[a]	Rapamune Following Cyclosporine Withdrawal[a]
Rapamune Dose (mg/day)		
Months 4 to 12	2.1 ± 0.7	8.2 ± 4.2
Months 12 to 24	2.0 ± 0.8	6.4 ± 3.0
Sirolimus $C_{min,}$ (ng/mL)[b]		
Months 4 to 12	10.7 ± 3.8	23.3 ± 5.0
Months 12 to 24	11.2 ± 4.1	22.5 ± 4.8

a: 215 patients were randomized to each group
b: Expressed by immunoassay and equivalence

The withdrawal of cyclosporine and concurrent increases in sirolimus trough concentrations to steady-state required approximately 6 weeks. Larger Rapamune® doses were required due to the absence of the inhibition of sirolimus metabolism and transport by cyclosporine and to achieve higher target concentrations during concentration-controlled administration following cyclosporine withdrawal.

Special Populations

Hepatic impairment: Sirolimus (15 mg) was administered as a single oral dose to 18 subjects with normal hepatic function and to 18 patients with Child-Pugh classification A or B hepatic impairment, in which hepatic impairment was primary and not related to an underlying systemic disease. Shown below are the mean ± SD pharmacokinetic parameters following the administration of sirolimus oral solution.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN 18 HEALTHY SUBJECTS AND 18 PATIENTS WITH HEPATIC IMPAIRMENT
(15 MG SINGLE DOSE – ORAL SOLUTION)

Population	$C_{max,ss}$[a] (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng•h/mL)	CL/F/WT (mL/h/kg)
Healthy subjects	78.2 ± 18.3	0.82 ± 0.17	970 ± 272	215 ± 76
Hepatic impairment	77.9 ± 23.1	0.84 ± 0.17	1567 ± 616	144 ± 62

a: As measured by LC/MS/MS

Compared with the values in the normal hepatic group, the hepatic impairment group had higher mean values for sirolimus AUC (61%) and $t_{1/2}$ (43%) and had lower mean values for sirolimus CL/F/WT (33%). The mean $t_{1/2}$ increased from 79 ± 12 hours in subjects with normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function. The rate of absorption of sirolimus was not altered by hepatic disease, as evidenced by C_{max} and t_{max} values. However, hepatic diseases with varying etiologies may show different effects and the pharmacokinetics of sirolimus in patients with severe hepatic dysfunction is unknown. Dosage adjustment is recommended for patients with mild to moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Renal impairment: The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites.

Pediatric: Limited pharmacokinetic data are available in pediatric patients. The table below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS WITH STABLE CHRONIC RENAL FAILURE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1, 3, 9, 15 MG/M^2 SINGLE DOSE)

Age Group (y)	n	t_{max} (h)	$t_{1/2}$ (h)	CL/F/WT (mL/h/kg)
5-11	9	1.1 ± 0.5	71 ± 40	580 ± 450
12-18	11	0.79 ± 0.17	55 ± 18	450 ± 232

Geriatric: Clinical studies of Rapamune did not include a sufficient number of patients >65 years of age to determine whether they will respond differently than younger patients. After the administration of Rapamune Oral Solution, sirolimus trough concentration data in 35 renal transplant patients >65 years of age were similar to those in the adult population (n = 822) 18 to 65 years of age. Similar results were obtained after the administration of Rapamune Tablets to 12 renal transplant patients >65 years of age compared with adults (n = 167) 18 to 65 years of age.

Gender: After the administration of Rapamune Oral Solution, sirolimus oral dose clearance in males was 12% lower than that in females; male subjects had a significantly longer $t_{1/2}$ than did female subjects (72.3 hours versus 61.3 hours). A similar trend in the effect of gender on sirolimus oral dose clearance and $t_{1/2}$ was observed after the administration of Rapamune Tablets. Dose adjustments based on gender are not recommended.

Race: In large phase 3 trials (Studies 1 and 2) using Rapamune Oral Solution and cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules), there were no significant differences in mean trough sirolimus concentrations over time between black (n = 139) and non-black (n = 724) patients during the first 6 months after transplantation at sirolimus doses of 2 mg/day and 5 mg/day. Similarly, after administration of Rapamune Tablets (2 mg/day) in a phase III trial, mean sirolimus trough concentrations over 6 months were not significantly different among black (n = 51) and non-black (n = 128) patients.

CLINICAL STUDIES

Rapamune® (sirolimus) Oral Solution: The safety and efficacy of Rapamune® Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials. These studies compared two dose levels of Rapamune Oral Solution (2 mg and 5 mg, once daily) with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporine and corticosteroids. Study 1 was conducted in the United States at 38 sites. Seven hundred nineteen (719) patients were enrolled in this trial and randomized following transplantation; 284 were randomized to receive Rapamune Oral Solution 2 mg/day, 274 were randomized to receive Rapamune Oral Solution 5 mg/day, and 161 to receive azathioprine 2-3 mg/kg/day. Study 2 was conducted in Australia, Canada, Europe, and the United States, at a total of 34 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized before transplantation; 227 were randomized to receive Rapamune Oral Solution 2 mg/day, 219 were randomized to receive Rapamune Oral Solution 5 mg/day, and 130 to receive placebo. In both studies, the use of antilymphocyte antibody induction therapy was prohibited. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The tables below summarize the results of the primary efficacy analyses from these trials. Rapamune Oral Solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the <0.025 level; nominal significance level adjusted for multiple [2] dose comparisons) at 6 months following transplantation compared with both azathioprine and placebo.

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STUDY 1[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day (n = 284)	Rapamune® Oral Solution 5 mg/day (n = 274)	Azathioprine 2-3 mg/kg/day (n = 161)
Efficacy failure at 6 months[c]	18.7	16.8	32.3
Components of efficacy failure			
Biopsy-proven acute rejection	16.5	11.3	29.2
Graft loss	1.1	2.9	2.5
Death	0.7	1.8	0
Lost to follow-up	0.4	0.7	0.6
Efficacy failure at 24 months	32.8	25.9	36.0
Components of efficacy failure			
Biopsy-proven acute rejection	23.6	17.5	32.3
Graft loss	3.9	4.7	3.1
Death	4.2	3.3	0
Lost to follow-up	1.1	0.4	0.6

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c. Primary endpoint

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 36 MONTHS FOR STUDY 2[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day (n = 227)	Rapamune® Oral Solution 5 mg/day (n = 219)	Placebo (n = 130)
Efficacy failure at 6 months[c]	30.0	25.6	47.7
Components of efficacy failure			
Biopsy-proven acute rejection	24.7	19.2	41.5
Graft loss	3.1	3.7	3.9
Death	2.2	2.7	2.3
Lost to follow-up	0	0	0
Efficacy failure at 36 months	44.1	41.6	54.6
Components of efficacy failure			
Biopsy-proven acute rejection	32.2	27.4	43.9
Graft loss	6.2	7.3	4.6
Death	5.7	5.9	5.4
Lost to follow-up	0	0.9	0.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c Primary endpoint

Patient and graft survival at 1 year were co-primary endpoints. The table below shows graft and patient survival at 1 and 2 years in Study 1 and 1 and 3 years in Study 2. The graft and patient survival rates were similar in patients treated with Rapamune and comparator-treated patients.

GRAFT AND PATIENT SURVIVAL (%) FOR STUDY 1 (12 AND 24 MONTHS) AND STUDY 2 (12 AND 36 MONTHS)[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1	(n = 284)	(n = 274)	(n = 161)	
Graft survival				
Month 12	94.7	92.7	93.8	
Month 24	85.2	89.1	90.1	
Patient survival				
Month 12	97.2	96.0	98.1	
Month 24	92.6	94.9	96.3	
Study 2	(n = 227)	(n = 219)		(n = 130)
Graft survival				
Month 12	89.9	90.9		87.7
Month 36	81.1	79.9		80.8
Patient survival				
Month 12	96.5	95.0		94.6
Month 36	90.3	89.5		90.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

The reduction in the incidence of first biopsy-confirmed acute rejection episodes in patients treated with Rapamune compared with the control groups included a reduction in all grades of rejection.

In Study 1, which was prospectively stratified by race within center, efficacy failure was similar for Rapamune Oral Solution 2 mg/day and lower for Rapamune Oral Solution 5 mg/day compared with azathioprine in black patients. In Study 2, which was not prospectively stratified by race, efficacy failure was similar for both Rapamune Oral Solution doses compared with placebo in black patients. The decision to use the higher dose of Rapamune Oral Solution in black patients must be weighed against the increased risk of dose-dependent adverse events that were observed with the Rapamune Oral Solution 5-mg dose (see **ADVERSE REACTIONS**).

PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Black (n = 166)	34.9 (n = 63)	18.0 (n = 61)	33.3 (n = 42)	
Non-black (n = 553)	14.0 (n = 221)	16.4 (n = 213)	31.9 (n = 119)	
Study 2				
Black (n = 66)	30.8 (n = 26)	33.7 (n = 27)		38.5 (n = 13)
Non-black (n = 510)	29.9 (n = 201)	24.5 (n = 192)		48.7 (n = 117)

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

Mean glomerular filtration rates (GFR) post transplant were calculated by using the Nankivell equation at 12 and 24 months for Study 1, and 12 and 36 months for Study 2. Mean GFR was lower in patients treated with cyclosporine and Rapamune Oral Solution compared with those treated with cyclosporine and the respective azathioprine or placebo control.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (Mean ± SEM, cc/min) BY NANKIVELL EQUATION POST TRANSPLANT[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Month 12	57.4 ± 1.3 (n = 269)	54.6 ± 1.3 (n = 248)	64.1 ± 1.6) (n = 149)	
Month 24	58.4 ± 1.5 (n = 221)	52.6 ± 1.5 (n = 222)	62.4 ± 1.9 (n = 132)	
Study 2				
Month 12	52.4 ± 1.5 (n = 211)	51.5 ± 1.5 (n = 199)		58.0 ± 2.1 (n = 117)
Month 36	48.1 ± 1.8 (n = 183)	46.1 ± 2.0 (n = 177)		53.4 ± 2.7 (n = 102)

a: Includes patients who prematurely discontinued treatment.
b. Patients who had a graft loss were included in the analysis with GFR set to 0.0.

Within each treatment group in Studies 1 and 2, mean GFR at one year post transplant was lower in patients who experienced at least 1 episode of biopsy-proven acute rejection, compared with those who did not.

Renal function should be monitored and appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated or increasing serum creatinine levels (see **PRECAUTIONS**).

Rapamune® Tablets: The safety and efficacy of Rapamune Oral Solution and Rapamune Tablets for the prevention of organ rejection following renal transplantation were compared in a randomized multicenter controlled trial (Study 3). This study compared a single dose level (2 mg, once daily) of Rapamune Oral Solution and Rapamune Tablets when administered in combination with cyclosporine and corticosteroids. The study was conducted at 30 centers in Australia, Canada, and the United States. Four hundred seventy-seven (477) patients were enrolled in this study and randomized before transplantation; 238 patients were randomized to receive Rapamune Oral Solution 2 mg/day and 239 patients were randomized to receive Rapamune Tablets 2 mg/day. In this study, the use of antilymphocyte antibody induction therapy was prohibited. The primary efficacy endpoint was the rate of efficacy failure in the first 3 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The table below summarizes the result of the efficacy failure analysis at 3 and 6 months from this trial. The overall rate of efficacy failure at 3 months, the primary endpoint, in the tablet treatment group was equivalent to the rate in the oral solution treatment group.

INCIDENCE (%) OF EFFICACY FAILURE AT 3 AND 6 MONTHS: STUDY 3[a,b]

	Rapamune® Oral Solution (n = 238)	Rapamune® Tablets (n = 239)
Efficacy Failure at 3 months[c]	23.5	24.7
Components of efficacy failure		
Biopsy-proven acute rejection	18.9	17.6
Graft loss	3.4	6.3
Death	1.3	0.8
Efficacy Failure at 6 months	26.1	27.2
Components of efficacy failure		
Biopsy-proven acute rejection	21.0	19.2
Graft loss	3.4	6.3
Death	1.7	1.7

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Efficacy failure at 3 months was the primary endpoint

Graft and patient survival at 12 months were co-primary endpoints. There was no significant difference between the oral solution and tablet formulations for both graft and patient survival. Graft survival was 92.0% and 88.7% for the oral solution and tablet treatment groups, respectively. The patient survival rates in the oral solution and tablet treatment groups were 95.8% and 96.2%, respectively.

The mean GFR at 12 months, calculated by the Nankivell equation, were not significantly different for the oral solution group and for the tablet group.

The table below summarizes the mean GFR at one-year post-transplantation for all patients in Study 3 who had serum creatinine measured at 12 months.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY NANKIVELL EQUATION AT 12 MONTHS POST TRANSPLANT: STUDY 3[a,b]

	Rapamune® Oral Solution	Rapamune® Tablets
Mean ± SEM	53.1 ± 1.7 (n = 229)	51.7 ± 1.7 (n = 225)

a: Includes patients who prematurely discontinued treatment
b. Patients who had a graft loss were included in the analysis with GFR set to 0.0.

In Study 4, the safety and efficacy of Rapamune as a maintenance regimen were assessed following cyclosporine withdrawal at 3 to 4 months post renal transplantation. Study 4 was a randomized, multicenter, controlled trial conducted at 57 centers in Australia, Canada, and Europe. Five hundred twenty-five (525) patients were enrolled. All patients in this study received the tablet formulation. This study compared patients who were administered Rapamune, cyclosporine, and corticosteroids continuously with patients who received the same standardized therapy for the first 3 months after transplantation (prerandomization period) followed by the withdrawal of cyclosporine. During cyclosporine withdrawal the Rapamune dosages were adjusted to achieve targeted sirolimus whole blood trough concentration ranges (20 to 30 ng/mL, experimental immunoassay). At 3 months, 430 patients were equally randomized to either Rapamune with cyclosporine therapy or Rapamune as a maintenance regimen following cyclosporine withdrawal. Eligibility for randomization included no Banff Grade 3 acute rejection episode or vascular rejection in the 4 weeks before random assignment; serum creatinine ≤ 4.5 mg/dL; and adequate renal function to support cyclosporine withdrawal (in the opinion of the investigator). The primary efficacy endpoint was graft survival at 12 months after transplantation. Secondary efficacy endpoints were the rate of biopsy-confirmed acute rejection, patient survival, incidence of efficacy failure (defined as the first occurrence of either biopsy-proven acute rejection, graft loss, or death), and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss, or death).

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, or patients with high panel of reactive antibodies (See **INDICATIONS AND USAGE**).

The table below summarizes the resulting graft and patient survival at 12, 24, and 36 months for this trial. At 12, 24, and 36 months, graft and patient survival were similar for both groups.

GRAFT AND PATIENT SURVIVAL (%): STUDY 4[a]

Parameter	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Graft Survival		
Month 12[b]	95.8	97.2
Month 24	91.2	93.5
Month 36	85.1	91.2
Patient Survival		
Month 12	97.2	98.1
Month 24	94.0	95.3
Month 36	88.4	93.5

a: Includes patients who prematurely discontinued treatment.
b: Primary efficacy endpoint.

The table below summarizes the results of first biopsy-proven acute rejection at 12 and 36 months. There was a significant difference in first biopsy-proven rejection between the two groups during post-randomization through 12 months. Most of the post-randomization acute rejections occurred in the first 3 months following randomization.

INCIDENCE OF FIRST BIOPSY-PROVEN ACUTE REJECTION (%) BY TREATMENT GROUP AT 36 MONTHS: STUDY 4[a]

Period	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine withdrawal (n = 215)
Prerandomization[b]	9.3	10.2
Postrandomization through 12 months[b]	4.2	9.8
Postrandomization from 12 to 36 months	1.4	0.5
Postrandomization through 36 months	5.6	10.2
Total at 36 months	14.9	20.5

a: Includes patients who prematurely discontinued treatment.
b: Randomization occurred at 3 months ± 2 weeks.

Patients receiving renal allografts with ≧ 4 HLA mismatches experienced significantly higher rates of acute rejection following randomization to the cyclosporine withdrawal group compared with patients who continued cyclosporine (15.3% vs 3.0%). Patients receiving renal allografts

with ≤ 3 HLA mismatches, demonstrated similar rates of acute rejection between treatment groups (6.8% vs 7.7%) following randomization.

The table below summarizes the mean calculated GFR in Study 4.

CALCULATED GLOMERULAR FILTRATION RATES (mL/min) BY NANKIVELL EQUATION AT 12, 24, AND 36 MONTHS POST TRANSPLANT: STUDY 4[a, b]

Parameter		Rapamune with Cyclosporine Therapy	Rapamune Following Cyclosporine Withdrawal
Month 12			
	Mean ± SEM	53.2 ± 1.5 n = 208	59.3 ± 1.5 n = 203
Month 24			
	Mean ± SEM	48.4 ± 1.7 n = 203	58.4 ± 1.6 n = 201
Month 36			
	Mean ± SEM	47.3 ± 1.8 (n = 194)	59.4 ± 1.8 (n = 194)

a: Includes patients who prematurely discontinued treatment.
b. Patients who had a graft loss were included in the analysis and had their GFR set to 0.0.

The mean GFR at 12 , 24, and 36 months, calculated by the Nankivell equation, was significantly higher for patients receiving Rapamune as a maintenance regimen following cyclosporine withdrawal than for those in the Rapamune with cyclosporine therapy group. Patients who had an acute rejection prior to randomization had a significantly higher GFR following cyclosporine withdrawal compared to those in the Rapamune with cyclosporine group. There was no significant difference in GFR between groups for patients who experienced acute rejection postrandomization.

INDICATIONS AND USAGE

Rapamune® (sirolimus) is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids. In patients at low to moderate immunological risk cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune® dose should be increased to reach recommended blood concentrations (See **DOSAGE AND ADMINISTRATION**).

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **CLINICAL STUDIES**)

CONTRAINDICATIONS

Rapamune is contraindicated in patients with a hypersensitivity to sirolimus or its derivatives or any component of the drug product.

WARNINGS

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see **ADVERSE REACTIONS**). Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections, and sepsis. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use Rapamune. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Increased serum cholesterol and triglycerides, that may require treatment, occurred more frequently in patients treated with Rapamune compared with azathioprine or placebo controls (see **PRECAUTIONS**).

In Studies 1 and 2, from month 6 through months 24 and 36, respectively, mean serum creatinine was increased and mean glomerular filtration rate was decreased in patients treated with Rapamune and cyclosporine compared with those treated with cyclosporine and placebo or azathioprine controls The rate of decline in renal function was greater in patients receiving Rapamune and cyclosporine compared with control therapies (see **CLINICAL STUDIES**).

Renal function should be closely monitored during the administration of Rapamune® in combination with cyclosporine since long-term administration can be associated with deterioration of renal function. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using other drugs which are known to impair renal function. In patients at low to moderate immunological risk continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients (see PRECAUTIONS).

In clinical trials, Rapamune has been administered concurrently with corticosteroids and with the following formulations of cyclosporine:

Sandimmune® Injection (cyclosporine injection)
Sandimmune® Oral Solution (cyclosporine oral solution)
Sandimmune® Soft Gelatin Capsules (cyclosporine capsules)
Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED])
Neoral® Oral Solution (cyclosporine oral solution [MODIFIED])

The efficacy and safety of the use of Rapamune in combination with other immunosuppressive agents has not been determined.

Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT):
The use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant recipients. Many of these patients had evidence of infection at or near the time of death.

In this and another study in de novo liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death.

Lung Transplantation – Bronchial Anastomotic Dehiscence:
Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when sirolimus has been used as part of an immunosuppressive regimen.

The safety and efficacy of Rapamune® (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.

PRECAUTIONS

General

Rapamune is intended for oral administration only.

Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with Rapamune. Appropriate post-operative measures should be considered to minimize this complication.

Lipids

The use of Rapamune® (sirolimus) in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment.

In Studies 1 and 2, in *de novo* renal transplant recipients who began the study with normal, fasting, total serum cholesterol (<200 mg/dL) or normal, fasting, total serum triglycerides (<200 mg/dL), there was an increased incidence of hypercholesterolemia (fasting serum cholesterol >240 mg/dL) or hypertriglyceridemia (fasting serum triglycerides >500 mg/dL), respectively, in patients receiving both Rapamune® 2 mg and Rapamune® 5 mg compared with azathioprine and placebo controls.

Treatment of new-onset hypercholesterolemia with lipid-lowering agents was required in 42 - 52% of patients enrolled in the Rapamune arms of Studies 1 and 2 compared with 16% of patients in the placebo arm and 22% of patients in the azathioprine arm.

In Study 4 during the prerandomization period, mean fasting serum cholesterol and triglyceride values rapidly increased, and peaked at 2 months with mean cholesterol values > 240 mg/dL and triglycerides > 250 mg/dL. After randomization mean cholesterol and triglyceride values remained higher in the cyclosporine withdrawal arm compared to the Rapamune® and cyclosporine combination.

Renal transplant patients have a higher prevalence of clinically significant hyperlipidemia. Accordingly, the risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Rapamune.

Any patient who is administered Rapamune should be monitored for hyperlipidemia using laboratory tests and if hyperlipidemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents, as outlined by the National Cholesterol Education Program guidelines, should be initiated.

In clinical trials, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates appeared to be well tolerated.

During Rapamune therapy with cyclosporine, patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the respective labeling for these agents.

Renal Function

Patients treated with cyclosporine and Rapamune were noted to have higher serum creatinine levels and lower glomerular filtration rates compared with patients treated with cyclosporine and placebo or azathioprine controls (Studies 1 and 2). The rate of decline in renal function in these studies was greater in patients receiving Rapamune and cyclosporine compared with control therapies. In patients at low to moderate immunological risk (See **CLINICAL STUDIES**) continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients. (see **WARNINGS**).

Renal function should be monitored during the administration of Rapamune® in combination with cyclosporine. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using agents (e.g., aminoglycosides, and amphotericin B) that are known to have a deleterious effect on renal function.

Antimicrobial Prophylaxis

Cases of *Pneumocystis carinii* pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for 1 year following transplantation.

Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough Rapamune concentration increases (see **ADVERSE REACTIONS**).

Information for Patients

Patients should be given complete dosage instructions (see **Patient Instructions**). Women of childbearing potential should be informed of the potential risks during pregnancy and that they should use effective contraception prior to initiation of Rapamune therapy, during Rapamune therapy and for 12 weeks after Rapamune therapy has been stopped (see **PRECAUTIONS: Pregnancy**).

Patients should be told that exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer (see **WARNINGS**).

Laboratory Tests

Whole blood sirolimus concentrations should be monitored in patients receiving concentration-controlled Rapamune. Monitoring is also necessary in patients likely to have altered drug metabolism, in patients ≥13 years who weigh less than 40 kg, in patients with hepatic impairment, and during concurrent administration of potent CYP3A4 inducers and inhibitors (see **PRECAUTIONS: Drug Interactions**).

Drug Interactions

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-glycoprotein. The pharmacokinetic interaction between sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

Cyclosporine capsules MODIFIED:

Rapamune Oral Solution: In a single dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus either simultaneously or 4 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, the mean C_{max} and AUC of sirolimus were increased by 116% and 230%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus C_{max} and AUC were increased by 37% and 80%, respectively, compared with administration of sirolimus alone.

Mean cyclosporine C_{max} and AUC were not significantly affected when sirolimus was given simultaneously or when administered 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). However, after multiple-dose administration of sirolimus given 4 hours after Neoral® in renal post-transplant patients over 6 months, cyclosporine oral-dose clearance was reduced, and lower doses of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) were needed to maintain target cyclosporine concentration.

Rapamune (sirolimus) Tablets: In a single-dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus (Rapamune Tablets) either simultaneously or 4 hours after a 300-mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, mean C_{max} and AUC were increased by 512% and 148%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after cyclosporine administration, sirolimus C_{max} and AUC were both increased by only 33% compared with administration of sirolimus alone.

Because of the effect of cyclosporine capsules (MODIFIED), it is recommended that sirolimus should be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED), (see DOSAGE AND ADMINISTRATION).

Cyclosporine oral solution: In a multiple-dose study in 150 psoriasis patients, sirolimus 0.5, 1.5, and 3 mg/m^2/day was administered simultaneously with Sandimmune® Oral Solution (cyclosporine Oral Solution) 1.25 mg/kg/day. The increase in average sirolimus trough concentrations ranged between 67% to 86% relative to when sirolimus was administered without cyclosporine. The intersubject variability (%CV) for sirolimus trough concentrations ranged from 39.7% to 68.7%. There was no significant effect of multiple-dose sirolimus on cyclosporine trough concentrations following Sandimmune® Oral Solution (cyclosporine oral solution) administration. However, the %CV was higher (range 85.9% - 165%) than those from previous studies.

Sandimmune® Oral Solution (cyclosporine oral solution) is not bioequivalent to Neoral® Oral Solution (cyclosporine oral solution MODIFIED), and should not be used interchangeably. Although there is no published data comparing Sandimmune® Oral Solution (cyclosporine oral solution) to SangCya® Oral Solution (cyclosporine oral solution [MODIFIED]), they should not be used interchangeably. Likewise, Sandimmune® Soft Gelatin Capsules (cyclosporine capsules) are not bioequivalent to Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) and should not be used interchangeably.

Diltiazem: The simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem. If diltiazem is administered, sirolimus should be monitored and a dose adjustment may be necessary.

Ketoconazole: Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of Rapamune® (sirolimus) Oral Solution, as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose sirolimus did not affect steady-state 12-hour plasma ketoconazole concentrations. It is recommended that sirolimus oral solution and oral tablets should not be administered with ketoconazole.

Rifampin: Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of sirolimus, greatly increased sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decreases in AUC and C_{max} of about 82% and 71%, respectively. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Drugs which may be coadministered without dose adjustment

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below. A synopsis of the type of study performed for each drug is provided. Sirolimus and these drugs may be coadministered without dose adjustments.

Acyclovir: Acyclovir, 200 mg, was administered once daily for 3 days followed by a single 10-mg dose of sirolimus oral solution on day 3 in 20 adult healthy volunteers.

Digoxin: Digoxin, 0.25 mg, was administered daily for 8 days and a single 10-mg dose of sirolimus oral solution was given on day 8 to 24 healthy volunteers.

Glyburide: A single 5-mg dose of glyburide and a single 10-mg dose of sirolimus oral solution were administered to 24 healthy volunteers. Sirolimus did not affect the hypoglycemic action of glyburide.

Nifedipine: A single 60-mg dose of nifedipine and a single 10-mg dose of sirolimus oral solution were administered to 24 healthy volunteers.

Norgestrel/ethinyl estradiol (Lo/Ovral®): Sirolimus oral solution, 2 mg, was given daily for 7 days to 21 healthy female volunteers on norgestrel/ethinyl estradiol.

Prednisolone: Pharmacokinetic information was obtained from 42 stable renal transplant patients receiving daily doses of prednisone (5-20 mg/day) and either single or multiple doses of sirolimus oral solution (0.5-5 mg/m^2 q 12h).

Sulfamethoxazole/trimethoprim (Bactrim®): A single oral dose of sulfamethoxazole (400 mg)/trimethoprim (80 mg) was given to 15 renal transplant patients receiving daily oral doses of sirolimus (8 to 25 mg/m^2).

Other drug interactions

Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the gut wall and liver. Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect this isoenzyme. Inhibitors of CYP3A4 may decrease the metabolism of sirolimus and increase sirolimus concentrations, while inducers of CYP3A4 may increase the metabolism of sirolimus and decrease sirolimus concentrations.

Drugs that may increase sirolimus blood concentrations include:

Calcium channel blockers: nicardipine, verapamil.
Antifungal agents: clotrimazole, fluconazole, itraconazole.
Macrolide antibiotics: clarithromycin, erythromycin, troleandomycin.
Gastrointestinal prokinetic agents: cisapride, metoclopramide.
Other drugs: bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

Drugs that may decrease sirolimus concentrations include:

Anticonvulsants: carbamazepine, phenobarbital, phenytoin.
Antibiotics: rifabutin, rifapentine.

This list is not all inclusive.

Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with Rapamune. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune and must not be used for dilution (see **DOSAGE AND ADMINISTRATION**).

Herbal Preparations

St John's Wort (*hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Since sirolimus is a substrate for both cytochrome CYP3A4 and P-glycoprotein, there is the potential that the use of **St. John's Wort in patients receiving Rapamune** could result in reduced sirolimus concentrations.

Vaccination

Immunosuppressants may affect response to vaccination. Therefore, during treatment with Rapamune, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

Drug-Laboratory Test Interactions

There are no studies on the interactions of sirolimus in commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Sirolimus was not genotoxic in the in vitro bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the in vivo mouse micronucleus assay.

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at dosages of 0, 12.5, 25 and 50/6 (dosage lowered from 50 to 6 mg/kg/day at week 31 due to infection secondary to immunosuppression) there was a statistically significant increase in malignant lymphoma at all dose levels (approximately 16 to 135 times the clinical doses adjusted for body surface area) compared with controls. In a second mouse study at dosages of 0, 1, 3 and 6 mg/kg (approximately 3 to 16 times the clinical dose adjusted for body surface area), hepatocellular adenoma and carcinoma (males), were considered Rapamune related. In the 104-week rat study at dosages of 0, 0.05, 0.1, and 0.2 mg/kg/day (approximately 0.4 to 1 times the clinical dose adjusted for body surface area), there was a statistically significant increased incidence of testicular adenoma in the 0.2 mg/kg/day group.

There was no effect on fertility in female rats following the administration of sirolimus at dosages up to 0.5 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area). In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg (approximately 4 to 11 times the clinical doses adjusted for body surface area). Reductions in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats following dosages of 0.65 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area) and above and in a monkey study at 0.1 mg/kg (approximately 0.4 to 1 times the clinical doses adjusted for body surface area) and above. Sperm counts were reduced in male rats following the administration of sirolimus for 13 weeks at a dosage of 6 mg/kg (approximately 12 to 32 times the clinical doses adjusted for body surface area), but showed improvement by 3 months after dosing was stopped.

Pregnancy

Pregnancy Category C: Sirolimus was embryo/feto toxic in rats at dosages of 0.1 mg/kg and above (approximately 0.2 to 0.5 the clinical doses adjusted for body surface area). Embryo/feto toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporine, rats had increased embryo/feto mortality compared with Rapamune alone. There were no effects on rabbit development at the maternally toxic dosage of 0.05 mg/kg (approximately 0.3 to 0.8 times the clinical doses adjusted for body surface area). There are no adequate and well controlled studies in pregnant women. Effective contraception must be initiated before Rapamune therapy, during Rapamune therapy, and for 12 weeks after Rapamune therapy has been stopped. Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

Use during lactation

Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from sirolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

The safety and efficacy of Rapamune in pediatric patients below the age of 13 years have not been established.

Geriatric use

Clinical studies of Rapamune Oral Solution or Tablets did not include sufficient numbers of patients aged 65 years and over to determine whether safety and efficacy differ in this population from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose adjustments based upon age in geriatric renal patients are not necessary.

ADVERSE REACTIONS

Rapamune® Oral Solution: The incidence of adverse reactions was determined in two randomized, double-blind, multicenter controlled trials in which 499 renal transplant patients received Rapamune Oral Solution 2 mg/day, 477 received Rapamune Oral Solution 5 mg/day, 160 received azathioprine, and 124 received placebo. All patients were treated with cyclosporine and corticosteroids. Data (≥ 12 months post-transplant) presented in the table below show the adverse reactions that occurred in any treatment group with an incidence of ≥ 20%.

Specific adverse reactions associated with the administration of Rapamune (sirolimus) Oral Solution occurred at a significantly higher frequency than in the respective control group. For both Rapamune Oral Solution 2 mg/day and 5 mg/day these include hypercholesterolemia, hyperlipemia, hypertension, and rash; for Rapamune Oral Solution 2 mg/day acne; and for Rapamune Oral Solution 5 mg/day anemia, arthralgia, diarrhea, hypokalemia, and thrombocytopenia. The elevations of triglycerides and cholesterol and decreases in platelets and hemoglobin occurred in a dose-related manner in patients receiving Rapamune.

Patients maintained on Rapamune Oral Solution 5 mg/day, when compared with patients on Rapamune Oral Solution 2 mg/day, demonstrated an increased incidence of the following adverse events: anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipemia, fever, and diarrhea.

In general, adverse events related to the administration of Rapamune were dependent on dose/concentration.

ADVERSE EVENTS OCCURRING AT A FREQUENCY OF ≥ 20% IN ANY TREATMENT GROUP IN PREVENTION OF ACUTE RENAL REJECTION TRIALS(%) AT ≥ 12 MONTHS POST-TRANSPLANTATION FOR STUDIES 1 AND 2[a]

Body System	Rapamune® Oral Solution ------2 mg/day------		Rapamune® Oral Solution -----5 mg/day-----		Azathioprine 2-3 mg/kg/day	Placebo
Adverse Event	Study 1 (n = 281)	Study 2 (n = 218)	Study 1 (n = 269)	Study 2 (n = 208)	Study 1 (n = 160)	Study 2 (n = 124)
Body As A Whole						
Abdominal pain	28	29	30	36	29	30
Asthenia	38	22	40	28	37	28
Back pain	16	23	26	22	23	20
Chest pain	16	18	19	24	16	19
Fever	27	23	33	34	33	35
Headache	23	34	27	34	21	31
Pain	24	33	29	29	30	25

Body System	Rapamune® Oral Solution ------2 mg/day------		Rapamune® Oral Solution -----5 mg/day-----		Azathioprine 2-3 mg/kg/day	Placebo
Adverse Event	Study 1 (n = 281)	Study 2 (n = 218)	Study 1 (n = 269)	Study 2 (n = 208)	Study 1 (n = 160)	Study 2 (n = 124)
Cardiovascular System						
Hypertension	43	45	39	49	29	48
Digestive System						
Constipation	28	36	34	38	37	31
Diarrhea	32	25	42	35	28	27
Dyspepsia	17	23	23	25	24	34
Nausea	31	25	36	31	39	29
Vomiting	21	19	25	25	31	21
Hemic And Lymphatic System						
Anemia	27	23	37	33	29	21
Leukopenia	9	9	15	13	20	8
Thrombocytopenia	13	14	20	30	9	9
Metabolic And Nutritional						
Creatinine increased	35	39	37	40	28	38
Edema	24	20	16	18	23	15
Hypercholesteremia (See **WARNINGS** and **PRECAUTIONS**)	38	43	42	46	33	23
Hyperkalemia	15	17	12	14	24	27
Hyperlipemia (See **WARNINGS** and **PRECAUTIONS**)	38	45	44	57	28	23
Hypokalemia	17	11	21	17	11	9
Hypophosphatemia	20	15	23	19	20	19
Peripheral edema	60	54	64	58	58	48
Weight gain	21	11	15	8	19	15
Musculoskeletal System						
Arthralgia	25	25	27	31	21	18
Nervous System						
Insomnia	14	13	22	14	18	8
Tremor	31	21	30	22	28	19

Body System	Rapamune® Oral Solution ------2 mg/day------		Rapamune® Oral Solution -----5 mg/day-----		Azathioprine 2-3 mg/kg/day	Placebo
Adverse Event	Study 1 (n = 281)	Study 2 (n = 218)	Study 1 (n = 269)	Study 2 (n = 208)	Study 1 (n = 160)	Study 2 (n = 124)
Respiratory System						
Dyspnea	22	24	28	30	23	30
Pharyngitis	17	16	16	21	17	22
Upper respiratory infection	20	26	24	23	13	23
Skin And Appendages						
Acne	31	22	20	22	17	19
Rash	12	10	13	20	6	6
Urogenital System						
Urinary tract infection	20	26	23	33	31	26

a: Patients received cyclosporine and corticosteroids.

With longer term follow-up, the adverse event profile remained similar. Some new events became significantly different among the treatment groups. For events which occurred at a frequency of • 20% by 24 months for Study 1 and 36 months for Study 2, only the incidence of edema became significantly higher in both Rapamune groups as compared with the control group. The incidence of headache became significantly more common in the Rapamune 5mg/day group as compared with control therapy.
At 24 months for Study 1, the following treatment-emergent infections were significantly different among the treatment groups: bronchitis, Herpes simplex, pneumonia, pyelonephritis, and upper respiratory infections. In each instance, the incidence was highest in the Rapamune 5 mg/day group, lower in the Rapamune 2 mg/day group and lowest in the azathioprine group. Except for upper respiratory infections in the Rapamune 5 mg/day cohort, the remainder of events occurred with a frequency of < 20%.

At 36 months in Study 2 only the incidence of treatment-emergent Herpes simplex was significantly different among the treatment groups, being higher in the Rapamune 5 mg/day group than either of the other groups.

The table below summarizes the incidence of malignancies in the two controlled trials for the prevention of acute rejection. At 24 (Study 1) and 36 months (Study 2) there were no significant differences among treatment groups.

INCIDENCE (%) OF MALIGNANCIES IN STUDIES 1 (24 MONTHS) AND STUDY 2 (36 MONTHS) POST-TRANSPLANT[a,b]

	Rapamune® Oral Solution 2 mg/day		Rapamune® Oral Solution 5 mg/day		Azathioprine 2-3 mg/kg/day	Placebo
Malignancy	Study 1 (n = 284)	Study 2 (n = 227)	Study 1 (n = 274)	Study 2 (n = 219)	Study 1 (n = 161)	Study 2 (n = 130)
Lymphoma/ lymphoproliferative disease	**0.7**	**1.8**	**1.1**	**3.2**	**0.6**	**0.8**
Skin Carcinoma						
Any Squamous Cell[c]	0.4	2.7	2.2	0.9	3.8	3.0
Any Basal Cell[c]	0.7	2.2	1.5	1.8	2.5	5.3
Melanoma	0.0	0.4	0.0	1.4	0.0	0.0
Miscellaneous/Not Specified	0.0	0.0	0.0	0.0	0.0	0.8
Total	**1.1**	**4.4**	**3.3**	**4.1**	**4.3**	**7.7**
Other Malignancy	**1.1**	**2.2**	**1.5**	**1.4**	**0.6**	**2.3**

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Patients may be counted in more than one category.

Among the adverse events that were reported at a rate of ≥3% and <20% at 12 months, the following were more prominent in patients maintained on Rapamune 5 mg/day, when compared with patients on Rapamune 2 mg/day: epistaxis, lymphocele, insomnia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome), skin ulcer, increased LDH, hypotension, facial edema.

The following adverse events were reported with ≥3% and <20% incidence in patients in any Rapamune treatment group in the two controlled clinical trials for the prevention of acute rejection, BODY AS A WHOLE: abdomen enlarged, abscess, ascites, cellulitis, chills, face edema, flu syndrome, generalized edema, hernia, *Herpes zoster* infection, lymphocele, malaise, pelvic pain, peritonitis, sepsis; CARDIOVASCULAR SYSTEM: atrial fibrillation, congestive heart failure, hemorrhage, hypervolemia, hypotension, palpitation, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation; DIGESTIVE SYSTEM: anorexia, dysphagia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, gum hyperplasia, ileus, liver function tests abnormal, mouth ulceration, **oral moniliasis, stomatitis; ENDOCRINE SYSTEM: Cushing's syndrome, diabetes mellitus,** glycosuria; HEMIC AND LYMPHATIC SYSTEM: ecchymosis, leukocytosis, lymphadenopathy, polycythemia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome); METABOLIC AND NUTRITIONAL: acidosis, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, dehydration, healing abnormal, hypercalcemia, hyperglycemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, lactic dehydrogenase increased, AST/SGOT increased, ALT/SGPT increased, weight loss; MUSCULOSKELETAL SYSTEM: arthrosis, bone necrosis, leg cramps, myalgia, osteoporosis, tetany; NERVOUS SYSTEM: anxiety, confusion, depression, dizziness, emotional lability, hypertonia, hypesthesia, hypotonia, insomnia, neuropathy, paresthesia, somnolence; RESPIRATORY SYSTEM: asthma, atelectasis, bronchitis, cough increased, epistaxis, hypoxia, lung edema, pleural effusion, pneumonia, rhinitis, sinusitis; SKIN AND APPENDAGES: fungal dermatitis, hirsutism, pruritus, skin hypertrophy, skin ulcer, sweating; SPECIAL SENSES: abnormal vision, cataract, conjunctivitis, deafness, ear pain, otitis media, tinnitus; UROGENITAL SYSTEM: albuminuria, bladder pain, dysuria, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, nocturia, oliguria, pyelonephritis, pyuria, scrotal edema, testis disorder, toxic nephropathy, urinary frequency, urinary incontinence, urinary retention.

Less frequently occurring adverse events included: mycobacterial infections, Epstein-Barr virus infections, and pancreatitis.

Among the events which were reported at an incidence of • •3% and < 20% by 24 months for Study 1 and 36 months for Study 2, tachycardi**a and Cushing's syndrome were reported** significantly more commonly in both Rapamune groups as compared with the control therapy. Events that were reported more commonly in the Rapamune 5 mg/day group than either the Rapamune 2 mg/day group and/or control group were: abnormal healing, bone necrosis, chills, congestive heart failure, dysuria, hernia, hirsutism. urinary frequency, and lymphadenopathy.

Rapamune® Tablets: The safety profile of the tablet did not differ from that of the oral solution formulation. The incidence of adverse reactions up to 12 months was determined in a randomized, multicenter controlled trial (Study 3) in which 229 renal transplant patients received Rapamune Oral Solution 2 mg once daily and 228 patients received Rapamune Tablets 2 mg once daily. All patients were treated with cyclosporine and corticosteroids. The adverse reactions that occurred in either treatment group with an incidence of ≥ 20% in Study 3 are similar to those reported for Studies 1 and 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of acne, which occurred more frequently in the oral solution group, and tremor which occurred more frequently in the tablet group, particularly in Black patients.

The adverse events that occurred in patients with an incidence of ≥3% and <20% in either treatment group in Study 3 were similar to those reported in Studies 1 and 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of hypertonia, which occurred more frequently in the oral solution group and diabetes mellitus which occurred more frequently in the tablet group. Hispanic patients in the tablet group experienced hyperglycemia more frequently than Hispanic patients in the oral solution group. In Study 3 alone, menorrhagia, metrorrhagia, and polyuria occurred with an incidence of ≥3% and <20%.

The clinically important opportunistic or common transplant-related infections were identical in all three studies and the incidences of these infections were similar in Study 3 compared with Studies 1 and 2. The incidence rates of these infections were not significantly different between the oral solution and tablet treatment groups in Study 3.

In Study 3 (at 12 months), there were two cases of lymphoma/lymphoproliferative disorder in the oral solution treatment group (0.8%) and two reported cases of lymphoma/lymphoproliferative disorder in the tablet treatment group (0.8%). These differences were not statistically significant and were similar to the incidences observed in Studies 1 and 2.

Rapamune following cyclosporine withdrawal: The incidence of adverse reactions was determined through 36 months in a randomized, multicenter controlled trial (Study 4) in which 215 renal transplant patients received Rapamune as a maintenance regimen following cyclosporine withdrawal and 215 patients received Rapamune with cyclosporine therapy. All patients were treated with corticosteroids. The safety profile prior to randomization (start of cyclosporine withdrawal) was similar to that of the 2-mg Rapamune groups in Studies 1, 2, and 3. Following randomization (at 3 months) patients who had cyclosporine eliminated from their therapy experienced significantly higher incidences of abnormal liver function tests (including increased AST/SGOT and increased ALT/SGPT), hypokalemia, thrombocytopenia, abnormal healing, ileus, and rectal disorder. Conversely, the incidence of hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia was significantly higher in patients who remained on cyclosporine than those who had cyclosporine withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal.

In Study 4, at 36 months, the incidence of Herpes zoster infection was significantly lower in patients receiving Rapamune following cyclosporine withdrawal compared with patients who continued to receive Rapamune and cyclosporine.

The incidence of malignancies in Study 4 is presented in the table below. In Study 4, the incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy was higher in patients receiving Rapamune plus cyclosporine compared with patients who had cyclosporine withdrawn.

INCIDENCE (%) OF MALIGNANCIES IN STUDY 4 AT 36 MONTHS POST-TRANSPLANT[a,b]

Malignancy	Nonrandomized (n = 95)	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Lymphoma/lymphoproliferative disease	**1.1**	**1.4**	**0.5**
Skin Carcinoma			
Any Squamous Cell[c]	1.1	1.9	2.3
Any Basal Cell[c]	3.2	4.7	2.3
Melanoma	0.0	0.5	0.0
Miscellaneous/Not Specified	1.1	0.9	0.0
Total	**4.2**	**6.5**	**3.7**
Other Malignancy	**1.1**	**3.3**	**1.4**

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Patients may be counted in more than one category.

Other clinical experience: Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the sirolimus trough concentration increases (see **PRECAUTIONS**).

There have been rare reports of pancytopenia.

Hepatotoxicity has been reported, including fatal hepatic necrosis with elevated sirolimus trough concentrations.

Abnormal healing following transplant surgery has been reported, including fascial dehiscence and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary).

OVERDOSAGE

Reports of overdose with Rapamune have been received; however, experience has been limited. In general, the adverse effects of overdose are consistent with those listed in the **ADVERSE REACTIONS** section (see **ADVERSE REACTIONS**).

General supportive measures should be followed in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral lethal dose was greater than 800 mg/kg.

DOSAGE AND ADMINISTRATION

It is recommended that Rapamune Oral Solution and Tablets be used initially in a regimen with cyclosporine and corticosteroids. Cyclosporine withdrawal is recommended 2 to 4 months after transplantation in patients at low to moderate immunological risk.

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES**).

Two-mg of Rapamune oral solution has been demonstrated to be clinically equivalent to 2-mg Rapamune oral tablets and hence, are interchangeable on a mg to mg basis. However, it is not known if higher doses of Rapamune oral solution are clinically equivalent to higher doses of tablets on a mg to mg basis. (See **CLINICAL PHARMACOLOGY: Absorption**). Rapamune is to be administered orally once daily.

Rapamune and cyclosporine combination therapy: The initial dose of Rapamune should be administered as soon as possible after transplantation. For *de novo* transplant recipients, a loading dose of Rapamune of 3 times the maintenance dose should be given. A daily maintenance dose of 2-mg is recommended for use in renal transplant patients, with a loading dose of 6 mg. Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg was used in clinical trials of the oral solution and was shown to be safe and effective, no efficacy advantage over the 2-mg dose could be established for renal transplant patients. Patients receiving 2 mg of Rapamune Oral Solution per day demonstrated an overall better safety profile than did patients receiving 5 mg of Rapamune Oral Solution per day.

Rapamune following cyclosporine withdrawal: Initially, patients considered for cyclosporine withdrawal should be receiving Rapamune and cyclosporine combination therapy. At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks and the Rapamune® dose should be adjusted to obtain whole blood trough concentrations within the range of 12 to 24 ng/mL (chromatographic method). Therapeutic drug monitoring should not be the sole basis for adjusting Rapamune therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy, and laboratory parameters. Cyclosporine inhibits the metabolism and transport of sirolimus, and consequently, sirolimus concentrations will decrease when cyclosporine is discontinued unless the Rapamune dose is increased. The Rapamune®

dose will need to be approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction (approximately 2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporine (approximately 2-fold increase).

Frequent Rapamune® dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once Rapamune® maintenance dose is adjusted, patients should be retained on the new maintenance dose at least for 7 to 14 days before further dosage adjustment with concentration monitoring. In most patients dose adjustments can be based on simple proportion: new Rapamune® dose = current dose x (target concentration / current concentration). A loading dose should be considered in addition to a new maintenance dose when it is necessary to considerably increase sirolimus trough concentrations: Rapamune® loading dose = 3 x (new maintenance dose - current maintenance dose). The maximum Rapamune® dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading **dose should be administered over 2 days. Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).**

To minimize the variability of exposure to Rapamune, this drug should be taken consistently with or without food. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune and must not be administered with Rapamune or used for dilution.

It is recommended that sirolimus be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED).

Dosage Adjustments

The initial dosage in patients ≥13 years who weigh less than 40 kg should be adjusted, based on body surface area, to 1 mg/m^2/day. The loading dose should be 3 mg/m^2.

It is recommended that the maintenance dose of Rapamune be reduced by approximately one third in patients with hepatic impairment. It is not necessary to modify the Rapamune loading dose. Dosage need not be adjusted because of impaired renal function.

Blood Concentration Monitoring

Whole blood trough concentrations of sirolimus should be monitored in patients receiving concentration-controlled Rapamune®. Monitoring is also necessary in pediatric patients, in patients with hepatic impairment, during concurrent administration of strong CYP3A4 and/or p-glycoprotein inducers and inhibitors, and/or if cyclosporine dosage is markedly changed or discontinued (see **DOSAGE AND ADMINISTRATION**).

In controlled clinical trials with concomitant cyclosporine (Studies 1 and 2), mean sirolimus whole blood trough concentrations through month 12 following transplantation, as measured by **immunoassay, were 9 ng/mL (range 4.5 – 14 ng/mL [10th** to 90th percentile]) for the 2 mg/day treatment group, and 17 ng/mL (range 10 - 28 ng/mL [10th to 90th percentile]) for the 5 mg/day dose.

In a controlled clinical trial with cyclosporine withdrawal (Study 4), the mean sirolimus whole blood trough concentrations during months 4 through 12 following transplantation, as measured

by immunoassay, were 10.7 ng/mL (range 6.3 - 16.0 ng/mL [10th to 90th percentile]) in the concomitant Rapamune and cyclosporine treatment group (n =205) and were 23.3 ng/mL (range **17.0 – 29.0 ng/mL [10th** to 90th percentile]) in the cyclosporine withdrawal treatment group (n = 200).

Results from other assays may differ from those with an immunoassay. On average, chromatographic methods (HPLC UV or LC/MS/MS) yield results that are approximately 20% lower than the immunoassay for whole blood concentration determinations. Adjustments to the targeted range should be made according to the assay utilized to determine sirolimus trough concentrations. Therefore, comparison between concentrations in the published literature and an individual patient concentration using current assays must be made with detailed knowledge of the assay methods employed. A discussion of the different assay methods is contained in *Clinical Therapeutics*, Volume 22, Supplement B, April 2000.

Instructions for Dilution and Administration of Rapamune® Oral Solution Bottles

The amber oral dose syringe should be used to withdraw the prescribed amount of Rapamune® Oral Solution from the bottle. Empty the correct amount of Rapamune from the syringe into only a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution. Stir vigorously and drink at once. Refill the container with an additional volume (minimum of four [4] ounces [1/2 cup, 120 mL]) of water or orange juice, stir vigorously, and drink at once.

Pouches

When using the pouch, squeeze the entire contents of the pouch into only a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution. Stir vigorously and drink at once. Refill the container with an additional volume (minimum of four [4] ounces [1/2 cup, 120 mL]) of water or orange juice, stir vigorously, and drink at once.

Handling and Disposal

Since Rapamune is not absorbed through the skin, there are no special precautions. However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes with plain water.

HOW SUPPLIED

Rapamune® (sirolimus) Oral Solution is supplied at a concentration of 1 mg/mL in:

1. Cartons:
   NDC # 0008-1030-06, containing a 2 oz (60 mL fill) amber glass bottle.
   NDC # 0008-1030-15, containing a 5 oz (150 mL fill) amber glass bottle.

In addition to the bottles, each carton is supplied with an oral syringe adapter for fitting into the neck of the bottle, sufficient disposable amber oral syringes and caps for daily dosing, and a carrying case.

2. Cartons:
   NDC # 0008-1030-03, containing 30 unit-of-use laminated aluminum pouches of 1 mL.
   NDC # 0008-1030-07, containing 30 unit-of-use laminated aluminum pouches of 2 mL.
   NDC # 0008-1030-08, containing 30 unit-of-use laminated aluminum pouches of 5 mL.

Rapamune® (sirolimus) Tablets are available as follows:

1 mg, white, triangular-shaped tablets **marked "RAPAMUNE 1 mg" on one side.**
NDC # 0008-1031-05, bottle of 100 tablets.
NDC # 0008-1031-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each).

2 mg, yellow to beige triangular-shaped tablets **marked "RAPAMUNE 2 mg" on one side.**
NDC # 0008-1032-05, bottle of 100 tablets.
NDC # 0008-1032-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each [2 x 5]).

Storage

Rapamune® Oral Solution bottles and pouches should be stored protected from light and refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be used within one month. If necessary, the patient may store both the pouches and the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., up to 24 hours for the pouches and not more than 15 days for the bottles).

An amber syringe and cap are provided for dosing and the product may be kept in the syringe for a maximum of 24 hours at room temperatures up to 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F). The syringe should be discarded after one use. After dilution, the preparation should be used immediately.

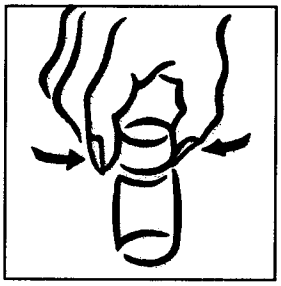
Rapamune Oral Solution provided in bottles may develop a slight haze when refrigerated. If such a haze occurs allow the product to stand at room temperature and shake gently until the haze disappears. The presence of this haze does not affect the quality of the product.

Rapamune® Tablets should be stored at 20° to 25°C (USP Controlled Room Temperature) (68° to 77°F). Use cartons to protect blister cards and strips from light. Dispense in a tight, light-resistant container as defined in the USP.

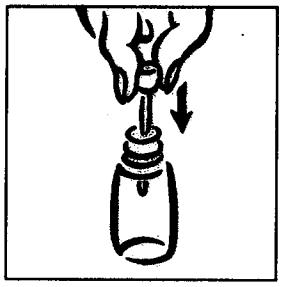
℞ only

US Pat. Nos.: 5,100,899; 5,212,155; 5,308,847; 5,403,833; 5,536,729.

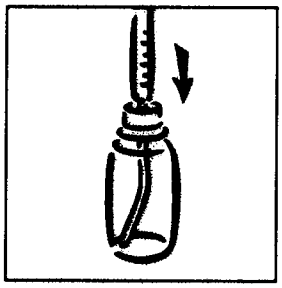
PATIENT INSTRUCTIONS FOR RAPAMUNE® (SIROLIMUS) ORAL SOLUTION ADMINISTRATION
Bottles



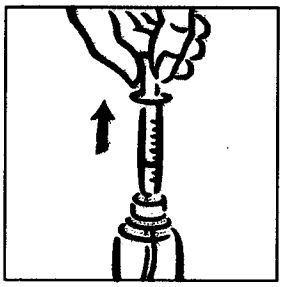
1. Open the solution bottle. Remove the safety cap by squeezing the tabs on the cap and twisting counterclockwise.



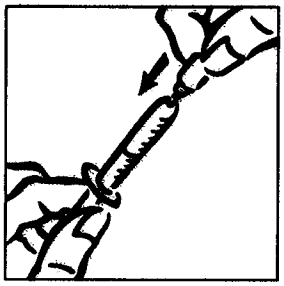
2. On first use, insert the adapter assembly (plastic tube with stopper) tightly into the bottle until it is even with the top of the bottle. Do not remove the adapter assembly from the bottle once inserted.



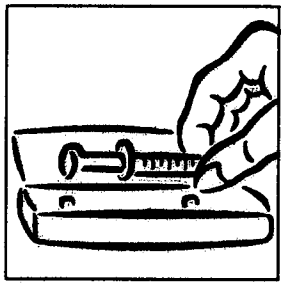
3. For each use, tightly insert one of the amber syringes with the plunger fully depressed into the opening in the adapter.



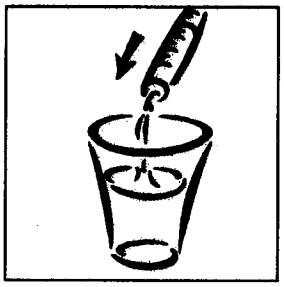
4. Withdraw the prescribed amount of Rapamune® (sirolimus) Oral Solution by gently pulling out the plunger of the syringe until the bottom of the black line of the plunger is even with the appropriate mark on the syringe. Always keep the bottle in an upright position. If bubbles form in the syringe, empty the syringe into the bottle and repeat the procedure.



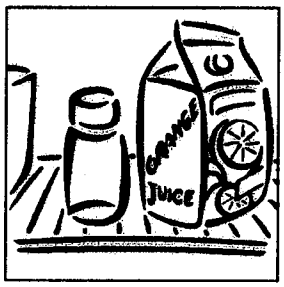
5. You may have been instructed to carry your medication with you. If it is necessary to carry the filled syringe, place a cap **securely on the syringe – the** cap should snap into place.



6. Then place the capped syringe in the enclosed carrying case. Once in the syringe, the medication may be kept at room temperature or refrigerated and should be used within 24 hours. Extreme temperatures (below 36°F and above 86°F) should be avoided. Remember to keep this medication out of the reach of children.

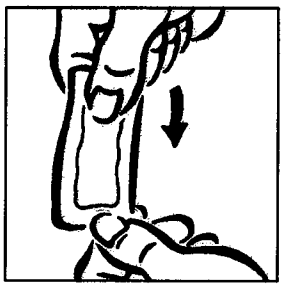


7. Empty the syringe into a glass or plastic cup containing at least 2 ounces (1/4 cup, 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice, or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution. The syringe and cap should be used once and then discarded.

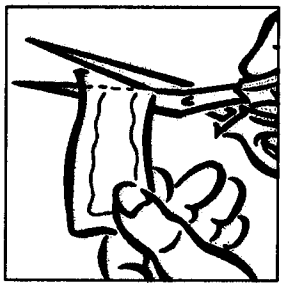


8. Always store the bottles of medication in the refrigerator. When refrigerated, a slight haze may develop in the solution. The presence of a haze does not affect the quality of the product. If this happens, bring the Rapamune® Oral Solution to room temperature and shake until the haze disappears. If it is necessary to wipe clean the mouth of the bottle before returning the product to the refrigerator, wipe with a dry cloth to avoid introducing water, or any other liquid, into the bottle.

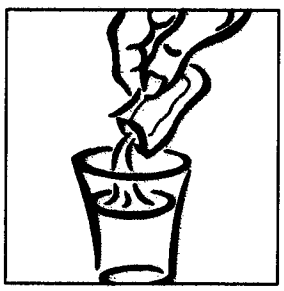
PATIENT INSTRUCTIONS FOR RAPAMUNE® (SIROLIMUS) ORAL SOLUTION ADMINISTRATION
Pouches



1. Before opening the pouch, squeeze the pouch from the neck area to push the contents into the lower part of the pouch.



2. Carefully open the pouch by folding the marked area and then cutting with a scissors along the marked line near the top of the pouch.



3. Squeeze the entire contents of the pouch into a glass or plastic cup containing at least 2 ounces (1/4 cup, 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution.

4. Unused pouches should be stored in the refrigerator.

Wyeth Laboratories
Division of Wyeth-Ayerst Pharmaceuticals Inc.
Philadelphia, PA 19101

W10431C001
ET01
Rev 01/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

MEDICAL REVIEW(S)

NDA 21-083/S-006
NDA 21-110/S-004

1. MEDICAL OFFICER REVIEW

Whyeth's Response to the February 8, 2002 Approvable Letter
NDA 21-083/S-006 and NDA 21-110/S-004

Rapamune® (Sirolimus)

Rapamune as a Maintenance Regimen Following Cyclosporine Withdrawal in Renal Transplantation

(This review includes a Rapamune® 3-year safety update on study 0468H1-310-GL)

Dates: Review submitted, completed
October 11, 2002, April 10, 2003.
Sponsor: Wyeth Pharmaceuticals
Name of Drug: Rapamune® (Sirolimus) Oral
Indication: Rapamune maintenance regimen following early cyclosporine (CsA) withdrawal in low to moderate risk renal transplant recipients.
Team Leader: M. Cavaille-Coll (HFD-590)
Medical Reviewer: A. Hernandez (HFD-590)
Biopharm: Jang-Ik Lee (HFD-590)
Statistical Reviewer: C. Dixon (HFD-725)
Project Manager: M. Bacho (HFD-590)

_____
Arturo Hernandez M.D.
Medical Officer, DSPIDP

Concurrences:

_____
Marc Cavaille-Coll, M.D. Ph.D.
Medical Team Leader, DSPIDP

_____
Renata Albrecht, M.D.
Division Director, DSPIDP

HFD-590/Original NDA's 21-083 (SRL's-010, -009,-008,-007BF,-007, -005, -005/NC)
21-110 (SRL's -010,-009,-007,-005/BF,-005,-001/NC, -001)
HFD-590/Division File
HFD-590/MO/AHernandez
HFD-590/Chem/MSeggel
HFD-590/Pharm/SKunder
HFD-590/RRO/RAnderson
HFD-590/PMTL/EFrank
HFD-590/PM/MBacho

2. TABLE OF CONTENTS *(page)*

[1] Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR. **Predicting glomerular filtration rate after kidney transplantation.** Transplantation. 59(12):1683-9, 1995.

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACM	Advisory Committee Meeting
ANCOVA	Analysis of covariance
AE	Adverse Events, Adverse reaction
AR	Acute rejection
ATG	Anti-thymocyte globulin
ATN	Acute tubular necrosis
AZA	Azathioprine
BCAR	Biopsy Confirmed Acute Rejection
CAD	Coronary Artery Disease
CsA	Cyclosporine
CI	Confidence interval
CInh	Calcineurin Inhibitor
CMH	Cochran-Mantel-Haenszel test
CsA	Cyclosporine
CV	Cardiovascular
DGF	Delayed graft function
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MMF	Mycophenolate mofetil
NDA	New Drug Application
NCEP-ATPIII	National Cholesterol Education Program - Adult Treatment Panel III
NHLBI	National Heart, Lung and Blood Institute
OKT3	A murine monoclonal antibody specific to the human CD3 complex
PTLD	Posttransplantation lymphoproliferative disorder
RMR	Rapamune Maintenance Regimen, Rapamune Maintenance Therapy.
S-	Study e.g. **S-310, S-212.** SCr Serum Creatinine.
SEM	Standard error of the mean.
SGOT/AST	Serum glutamic oxaloacetic transaminase/aspartate aminotransferase
SGPT/ALT	Serum glutamate pyruvate transaminase/alanine aminotransferase
SRL	Sirolimus
SRL-2 group	Sirolimus 2 mg dose group, Refer to **S-301** and **S-302** groups
SRL-5 group	Sirolimus 5 mg dose group, Refer to **S-301** and **S-302** groups
Conc Ctrl	Concentration controlled
TEAE	Treatment-emergent adverse event
TMFAS	Table Modified from Applicant's Submission
TTP	Thrombotic thrombocytopenic purpura
VFE	Valid-for-efficacy
WBC	White Blood Cells

4. DEFINITIONS:

Acute Rejection Episodes(BCAR): They were biopsy-confirmed using the Banff 1993 criteria.

Cyclosporine withdrawal studies = Cyclosporine elimination studies = Studies 310 and 212.

Cyclosporine withdrawal group = Cyclosporine elimination group = Group B

Efficacy failure was defined as the first occurrence of acute rejection, graft loss, or death. (**S-310**)

Group A: This group received sirolimus, CsA and corticosteroids. We will refer to this group also as SRL + CsA group or Rapamune fixed dose maintenance regimen

Group B: This group withdrawal CsA at 3 or 4 months posttransplantation. We will refer to this group also as SRL group, CsA withdrawal group or Sirolimus concentration controlled maintenance regimen group.

Graft loss:
S-310: Graft loss was defined as physical loss (nephrectomy), functional loss (necessitating maintenance dialysis for > 8 weeks), re-transplant, lost to follow-up, or death.
S-301 and 302: Graft loss was defined as any one of the following: 1) more than 56 consecutive days of dialysis, 2) nephrectomy of the transplanted organ, 3) requirement for retransplantation, or 4) death with functioning graft.

Late primary BCAR: Late primary BCAR was defined as follows:
S-301, BCAR after 90 posttransplantation.
S-302, BCAR after 120 days posttransplantation.
S-310, BCAR 12±2 week posttransplantation.

Non-significant, was not significant, etc.: This term is used to denote "not statistically significant"

Treatment failure was the first occurrence of acute rejection, graft loss, death, or premature discontinuation. (**S-310**)

Valid-for-efficacy (VFE population). E.g. In **S-212** patients completing 6 months on protocol-designated therapy without having experienced an acute rejection were considered VFE

5. EXECUTIVE SUMMARY

5.1. BACKGROWND:

This review evaluates whether the submitted data support the approval of concentration-controlled sirolimus with early CsA withdrawal in low-to-moderate risk renal allograft recipients as an effective immunosuppression maintenance regimen, and whether the benefits of early CsA elimination with the favorable decrease in CsA-associated toxicities outweigh the risks associated with increased sirolimus exposure.

Rapamune® oral solution was first FDA-approved on September 15, 1999 (NDA 21-083). In August 25, 2000 the 1mg tablet (NDA 21-110) and in August 22, 2002 the 2mg tablet were approved. The basis for this approval were studies 301 and 302 (randomized, double-blind, phase III studies) Both studies compared Rapamune®, 2 mg and 5 mg, to azathioprine or placebo respectively and demonstrated the non-inferiority of Rapamune® with respect to 12-month patient and graft survival. In these studies, a significant reduction in the incidence of rejection at 6 months was observed. However, renal function was markedly decreased at 12 months in the sirolimus treatment groups compared to controls[2].

The approved package insert recommends the use of this product in combination with cyclosporine and corticosteroids for the prophylaxis of organ rejection in patients receiving renal allografts. In April 2001 Wyeth Pharmaceuticals Inc. submitted supplemental application for the use of Rapamune ® (sirolimus) Oral Solution and Tablets within an immunosuppressive regimen that would allow for cyclosporine withdrawal. The new proposed indication was supported by pivotal study 310-GL
and supportive study 212-US (Cyclosporine withdrawal clinical studies). These studies evaluated the Rapamune plus cyclosporine combination versus a cyclosporine-withdrawal arm. In this arm, cyclosporine is withdrawal from the immunosuppressive regimen at 2-4 months post-transplantation, and Rapamune® dose is increased and adjusted to target trough sirolimus concentrations of 20-30 ng/ml for study 310, and 10 to 20 ng/ml for 212 (by Immunoassay) during the first 12 months after CsA withdrawal.

The January 24, 2002-ACM members addressed the supplemental NDA and recommended to identify the renal transplant population who would most benefit from sirolimus concentration-controlled with early cyclosporine withdrawal regimen as well as
to determine the minimum efficacious and maximal tolerated sirolimus concentrations and method of therapeutic drug monitoring (TDM).
The advisory committee members also expressed concern over whether there was sufficient information provided to define in the label the population that could benefit from such a regimen. Lack of adequate representation of patients from all demographic categories of renal transplants in the U.S. heightened these concerns.

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[2] During these studies, the whole blood cyclosporine concentration levels remained at or above the upper limit of the target concentration. Therefore, phase IV commitments were agreed to evaluate the optimum therapeutic range for sirolimus, to report long term follow-up safety and efficacy data from studies 301 and 302. Including an intent to treat analysis on GFR and serum creatinine (February 08, 2002 FDA-approvable letter)

The initial submission for the Rapamune® maintenance regimen (RMR) analyzed the outcome at 24 months. The numbers of deaths and graft losses were similar between groups A and B. However the number of discontinuations was higher in group B compared with group A. This difference raises the concern about the significance and impact of these differences on the safety conclusion drawn from this study.
Under these circumstances, FDA issued an approvable letter on February 08, 2002. In this letter, the sponsor was asked to confirm the safety and efficacy of the proposed regimen, address the ACM concerns and to complete all the post-marketing commitments established in the September15, 1999-approval letter for Rapamune® oral solution.

On 29 Jul 2002, a pre-submission meeting was held to review the proposed Wyeth's response to the 08 Feb 2002 FDA-approvable letter for the CsA-withdrawal indication.
FDA noted that studies 0468H1-316-GL (renal conversion study) and 0468H1-101164-US (high-risk study) were not completed. However, Wyeth's justification to resubmit was accepted because of the potential benefits to the transplant population from the proposed regimen.
FDA acknowledged Wyeth's re-submission on October 11, 2002 and it was considered complete, class 2 response to our February 8, 2002 action letter (User fee goal date: April 15, 2003).

Additionally, on January 31, 2003 the applicant submitted a major clinical amendment including a 3-years safety summary from study 310. The main purpose of this amendment was to include the 3-year data in the package insert at the time of approval.

5.2. STATEMENT OF CONCLUSIONS:

Conclusions are mainly based on S-310, when conclusions are drawn from other studies, they will be specified in the text. Long term data on S-301 and S-302 and 3-years safety summary from study 310 are integrated in this summary.

Patient and Graft Survival:

- ***Patient survival was adequate and similar in both S-310 and S-212 and across treatment arms (94-97% range).***
- ***The rates in graft survival were similar at 24 and 36 months across treatment arms. Three-year safety update on S-310, showed an increasing difference in graft survival across treatment favoring group B. According to protocol specified statistical parameters, graft survival in group B is not inferior compared to group A (A - B = -6.0%: 95% CI= -12.1 , 0.0)***
- ***Patient survival in studies 301 and 302 showed no statistically significant difference across the treatment groups in both studies.***
- ***In S-301 and 302 Graft survival ranged from 80% to 90% and there was no significant difference in the rate of graft survival across arms in both studies.***
- ***The most common causes of death were due to infection and cardiovascular events in both S-301 and 302.***

Infections

- *Culture, serology or biopsy was not required to document or include an event as a TEAE related to infection. Therefore, results regarding etiology should be evaluated with caution.*
- *The type and number of infections were similar in both S-310 and S212 and across arms.*
- *Excluding herpes zoster and Fungal dermatitis, there were no significant differences across arms in the rates of infections and severe life threatening infections by The COSTART system*
- *Higher rates in herpes zoster infection in group A, S-310 and fungal dermatitis in group B, S-212 were observed. However, the clinical impact of these differences is not a major concern.*
- *Herpes zoster infection rate, reported as TEAE, was significantly higher in group A (6.5%) than in group B (0.9%), p = 0.004. Pneumonia rates were significantly higher in group B at 12 months. This rate was no longer significant at 36 months (14.4% versus 9.3%, group B versus group A, p = 0.135).*
- *The etiology of the pneumonia was not identified in 67 % of the cases (27 out of 41 cases in both groups). Deaths occurred in 9.7%, 2 cases in each group. Anti-infective therapy was effective in the remaining 37 cases.*
- *Herpes simplex was significantly higher in SRL-5 than the SRL-2 group in S-301 or SRL-2 group and placebo in S-302*
- *Pneumonia was a common infection among S-301 and S-302 and across arms. It was numerically higher in SRL-5 and SRL2 in studies S-301 and S-302, respectively.*

Malignancies

- *Squamous and basal cell carcinomas were the most frequently reported malignancies in studies 310, 212, 301 and 302. The differences in the incidence of malignancies between either sirolimus dose group or control group were not statistically significant in both S-301 and S-302*
- *TEAE rates related to malignancies at 36 months were 11.2% versus 5.6% group A versus group B, respectively, p = 0.054*
- *Basal cell carcinoma*[3] (BCC) *was the most frequently reported malignancy in group A (4.7% versus 2.3%, group A versus groups B, respectively). These types of skin cancers are non-aggressive and are highly curable. On the other hand Squamous cell carcinomas*[4] *(SCCs), were more frequent in group B (1.9% versus 2.3%, group A versus group B, respectively. However, they are more clinically significant because of their ability to metastasize, even though they are also highly curable when detected and treated early. In summary, SCC is clinically more relevant than BCC.*
- *Four cases of Lymphoma / lymphoproliferative disease were reported, three of them in group A. We cannot draw any definitive conclusions based on this 4 cases.*

[3] *This type of cancer accounts for 70 to 80% of non-melanoma skin cancers in the general population.*
[4] *This type of malignancy accounts for 20% of non-melanoma skin cancers in the general population.*

Acute Rejection:

- ***First BCAR was numerically higher in the cyclosporine withdrawal arm compared with the CsA + SRL group and severity of rejection was similar between two groups. After cyclosporine withdrawal (group B), there was a transient increase in the number of BCAR episodes. This increased rate of AR, although not statistically significant and mild to moderate in severity, is clinically relevant because it implies at least additional treatment with steroids. It is well known that AR is an important risk factor for chronic rejection. AR episodes occurring after 3 or 6 months confer the greatest risk for chronic rejection and late renal graft loss according to published data[5],[6]. However, at 12 and 36 month follow-up (studies 212 and 310, respectively), numerically higher rates of acute rejection in group B did not result in a significantly lower graft survival. On the contrary group B had numerically lower graft losses.***

Sub-populations:

- ***As expected, patients with higher degree of HLA mismatches had a higher rate of BCAR. Patients with > 3 HLA mismatches presented significantly higher first BCAR rates in the CsA withdrawal arm (15.3%) compared with group A (3.0%), p = 0.018. It is well known that acute rejection has a negative impact on renal function and long-term graft survival. Interestingly, the increased incidence of primary BCAR was not associated with a detectable decrease in graft survival. Renal function was superior in the CsA withdrawal arm compared to the CsA + SRL group regardless of the degree of HLA mismatch. We agree with the applicant that this sub-population could also benefit from the CsA withdrawal and RMR. However, long term data on renal function, patient and graft survival at 5 years posttransplantation will further validate or disprove the 3-years data findings.***
- ***As expected, higher rates of BCAR were observed in black patients compared with non black in both groups A and B, but the differences observed in groups A versus B were not statistically significant.***
  Study 310 was not conducted in USA and did not adequately represent all sub-populations. African American and Hispanic populations were underrepresented in the CsA elimination studies. Even though, S-212 had a better representation of the African American population (19% in group A and 15% in group B) we cannot recommend the CsA elimination regimen for these sub populations due to the limitations of such a small database. On the other hand we cannot exclude the possibility that that AA and Hispanic patients with a low immunologic risk[7] could be suitable candidates for CsA withdrawal and RMR.
- ***Data on children and elderly is limited and definitive conclusions cannot be drawn.***

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[5] Humar A, Kerr S, Gillingham KJ, et al. Features of acute rejection that increase risk for chronic rejection. Transplantation 1999; 68: 1200–1203.

[6] Yvo w. J. Sijpkens, Ilias I. N. Doxiadis et al. Early versus late acute rejection episodes in renal transplantation Transplantation 2003; 75: 204–208.

[7] Demonstrated by lack of BCAR episodes during the first three months posttransplantation, for example.

Renal Function:

- *The ITT and on-therapy analyses demonstrated better GFR among CsA withdrawn patients compared with patients who continued on CsA plus sirolimus combination (S-212 and S-310). We agree with the applicant that CsA withdrawal, in the populations studied, is associated with superior renal function through 36 months posttransplantation compared with the patients that continue on CsA + SRL combination.*
- *ITT analysis showed that the difference in mean slopes of GFR over time between groups (A-B) was statistically significant from 6 to 36 and 12 to 36 month periods. The main contributing factor for the difference between group slopes is the deterioration in renal function over time in the CsA + SRL group (A significantly negative slope change in group A and a numerically positive the mean slopes change in group B)*
- *We agree with the sponsor that the baseline quartile analysis supports that all group B randomized patients might benefit from CsA elimination, irrespective of their baseline renal function.*
- *We agree with the sponsor that the findings from the studies 301, 302, and 309 and CsA withdrawal studies 310 and 212 (On therapy and ITT analysis) corroborates that renal function decreases over time with a SRL+ CsA regimen suggesting a CsA-associated nephrotoxicity which is exacerbated by its co-administration with sirolimus. These findings were numerically and /or significantly more pronounced, for patients receiving the 5-mg/day dose of sirolimus than for those receiving the 2-mg/day dose of sirolimus suggesting a dose related effect on cyclosporine nephrotoxicity.*

Discontinuations:

- *Discontinued patient demographic characteristics in groups A and B were not significantly different (Sex, ethnicity, age, height, weight, primary or secondary Transplant, CMV status, HLA mismatches, and Primary etiology of ESRD) in both studies 310 and 212.*
- *During the first year in S-310, more patients discontinued from the CsA withdrawal arm. However, by the end of the third year, the trend reversed.*
- *S-310 36-months data analysis showed that discontinuation rates were significantly higher in group A (48% vs. 38 % groups A vs B, respectively, P=0.041). In contrast, S-212 discontinuation rate was higher in group B, but not significantly different from group A. 26% vs 21%, respectively. The observed differences between treatment groups are not clinically relevant.*
- *Adverse reactions were the most common cause of discontinuation in both S-310 and S-212.*
- *In S-310, CsA toxicity was the main Adverse Event Leading to Premature Withdrawal (AELPW), and it was significantly higher in group A (4%) vs. group B (0%), p = 0.007. Study 212 showed no significant differences in AELPW.*
- *On therapy laboratory assessment was complemented with Completers, and LOCF analysis since laboratory data was available only for 30 days following patient discontinuation.*
- *There were no clinically meaningful differences between the different type of statistical analyses. The differences observed between groups A and B are expected as a result of treatment effects.(e.g. CsA related toxicity events in group A)*
- *In conclusion, ITT, completers, LOCF, and last values on therapy analyses complemented the on-therapy analyses. Similar conclusions are drawn from all types of analyses and we*

agree with the applicant that lost or discontinued patients have not introduced bias that could have impacted on the safety conclusions drawn from on therapy analyses.

The Impact of Rejection on Renal Function

- *Acute rejection was associated with decreased renal function in all randomized cohorts in studies 310, 212, 301,and 302 (Including the comparator groups azathioprine and placebo). The impact was more pronounced among patients randomly assigned to receive the combination of CsA + SRL, particularly at a higher dose. Similarly, remaining rejection free was associated with better renal function in these studies.*
- *In both S-310 and 212, patients who experienced BCAR post-transplantation showed a significantly lower mean GFR in both randomized cohorts compared to those who were rejection free. As expected, acute rejection has a deleterious effect on GFR that is amplified if the patients continue in the CsA + SRL combination.*
- *After randomization[8], patients in S-310 group B that experience primary BCAR showed a numerical but not significant benefit in mean GFR compared to the patients who continued on CsA + SRL (Group A). Similarly, in S-212 patients who were randomized to the CsA withdrawal arm and rejected, showed similar mean GFR as patients randomized to group A and experience primary BCAR. (Group B/rejectors, 45.4 ±4 mL/min versus group A/rejectors 44.9 ±5.7 mL/min, P=0.943).*
- *Even though, there was a significant GFR benefit among the rejectors randomized to the CsA withdrawal arm in S-310, the data from S-212 do not support this observation. Therefore we can conclude that the potential benefit of CsA withdrawal benefit on GFR among rejectors was not clearly demonstrated. The results suggest that the impact of AR on renal function may override the salutary effects of CsA withdrawal as a result of kidney damage during the rejection event.*
- *Studies 301 and 302 showed that renal function was numerically and/or significantly lower among patients who experienced BCAR who were randomly assigned to SRL + CsA combination (at 2 and 5 mg doses) compared with that of the corresponding rejector subsets assigned to AZA (S-301) or placebo (S-302).*

Characterization of Rejection Patterns

- *It is difficult to compare the rejection patterns among studies 301, 302, and 310 because of differences in study design (time of randomization, type of patients enrolled etc.).*
- *Regardless of the enrollment imbalances among treatment arms in S-301, S-302 and S-310, there was a disproportionate high number of late BCAR in the CsA + SRL groups compared with Aza, Placebo and CsA withdrawal arms, respectively.*
- *A major contributing factor was not clearly identified (e.g. Race, degree of HLA mismatch, demographic characteristics, and on-therapy status) to explain the pattern of late BCAR observed in these studies. However, in studies 301, 302 and 310, the CsA + SRL combination presented a similar pattern of "late primary BCAR's", which are in greater number than in the Aza, placebo or CsA withdrawal arms.*

[8] **S-310:** Randomization occurred 12±2 weeks after surgery and CsA withdrawal @ 3-4th months after surgery

- *Partial analyses e.g. 12 to 36 months in S-310 will give a false perspective of the primary BCAR rates, favoring the CsA withdrawal arm with less rejection episodes when in reality the overall rate is higher in this arm. Further investigation is required to understand the long-term effect of the late acute rejection patterns in the CsA withdrawal regimens.*

Fasting Serum Lipids:

- *Dyslipoproteinemia was routinely treated in the study population; therefore, the studies results reflect the effect of the therapeutic intervention.*
- *There was rapid increase in the cholesterol and triglycerides levels in the pre-randomization phase S-310, suggesting a drug related (Rapamune + CsA) effect.*

- *The cholesterol and triglycerides levels were persistently above the recommended levels despite therapeutic intervention occurring during the study (Including statins and other drugs). These levels were higher or significantly higher in the CsA elimination arm, group B, and were associated with an increased sirolimus exposure.*
- *CsA withdrawal with a concomitant increase in Rapamune®dose, does not provide any improvement for the patient's dyslipoproteinemia. On the contrary, it may require an increase in dose of the lipid-lowering agent or the addition of another agent.*

Liver Function Tests and Other Hematological Parameters:

- *Serum aminotransferases and LDH presented significantly higher mean values in group B. Also more group B patients discontinued due to hepatic-related events (1 versus 6 patients, group A versus group B).*
- *The mean hemoglobin concentration and mean platelet counts were lower in the CsA withdrawal arm. These differences were not clinically significant.*

Blood Pressure:

- *In S310, mean systolic and diastolic blood pressures were significantly better in Group B patients from 6 through 36 months follow up. This benefit was not observed in patients from S-212 in which mean systolic and diastolic pressures were quite similar across arms and through out the study period.*

5.3. POPULATION THAT MAY BENEFIT FROM RAPAMUNE® MAINTINANCE REGIMEN WITH EARLY CYCLOSPORINE WITHDRAWAL

The concentration-controlled Rapamune® maintenance regimen (RMR) with cyclosporine withdrawal at 2 to 4 months posttransplantation is proposed for renal allograft recipients with low-to-moderate immunologic risk for acute rejection.
Patients at low to moderate risk for rejection were defined by the enrollment criteria and by their clinical course during the first 2 to 4 months posttransplantation (Study 310).
By definition this selected sub-population would require less immunosuppression compared with high-risk patients.

According to the characteristics of US renal transplant population and taking into consideration the inclusion / exclusion criteria used in the S-310 and S-212 we can conservatively assume that more than 50% of the US renal transplant patients would be eligible for the proposed regimen.

Patients in study 310 were eligible to undergo randomization at 3 months (±2 weeks) to either continue combination therapy with CsA and sirolimus or to initiate CsA withdrawal, unless they met one of the following criteria.
Banff grade III acute rejection or vascular rejection within the 4 weeks prior to CsA withdrawal, Dialysis-dependency, Serum creatinine > 4.5 mg/dL(> 400 µmol/L) and patients with inadequate renal function to support CsA withdrawal (in the opinion of the investigator).

Inclusion/exclusion criteria in S-310 allowed 82% (430/525) of the population to be eligible for CsA withdrawal RMR. The discontinuation rate in the CsA withdrawal arm was 38% (81/215) at 36 months (Mainly due to adverse reactions and unsatisfactory response to the treatment).
Therefore, we could expect that ≈62% of selected patients according to S-310 inclusion/exclusion criteria would potentially receive a long-term benefit from the proposed regimen.
The Rapamune with CsA withdrawal regimen maintains high patient and graft survival.
However, there are an increased number of acute rejection episodes after CsA withdrawal. Most of these episodes of acute rejection occurred during the first 3 months following CsA withdrawal.
Long-term renal function data from Studies 301 and 302, in which patients received the Rapamune + CsA combination, continue to demonstrate decreased renal function compared with control therapies (Azathioprine and Placebo).
In S-310, despite of the increased number in acute rejection episodes in the CsA withdrawal arm, the long-term renal function of patients on RMR following CsA withdrawal is superior compared with patients who continued on Rapamune + CsA combination.

5.4. Summary of Relevant Comments:

- ***We agree with the sponsor that the findings from the studies 301, 302, and 309 and CsA withdrawal studies 310 and 212 (On therapy and ITT analysis) corroborates that renal function decreases over time with a SRL+ CsA regimen suggesting a CsA-associated nephrotoxicity which is exacerbated by its co-administration with sirolimus. These findings were numerically and /or significantly more pronounced, for patients receiving the 5-mg/day dose of sirolimus than for those receiving the 2-mg/day dose of sirolimus suggesting a dose related effect on cyclosporine nephrotoxicity. Therefore,***
- ***This is first cyclosporine-sparing regimen for kidney transplant patients that will be approved in USA.***
- ***More than one-half of all new kidney transplant patients could potentially benefit from this newly approved regimen.***
- ***S-310 showed similar graft and patient survival at 12, 24 and 36 months after transplantation, in both groups. RMR with CsA withdrawal at 2-4 months post kidney transplantation will allow improving GFR. The numerically increased number in BCAR episodes after CsA withdrawal, do not have a detrimental impact on mean renal function or graft survival after 36 months (S-310). Therefore it is likely that RMR to be associated with long-term improved kidney function. Although, the group assigned to CsA withdrawal benefited as a whole from improved renal function;***
- ***Additional data is required to support the use of this regimen in the high risk and under represented populations[9]. (Black recipients, Re-transplants, Multiorgan transplants, High panel-reactive antibodies and patients with Banff Grade III acute rejection episode or vascular rejection prior to CsA withdrawal)***
-

5.5. Risks/benefits:

The benefits of concentration-controlled sirolimus with CsA withdrawal includes improvement in renal function, and improved graft survival when compared to the CsA + SRL maintenance regimen. Also a decrease in the incidence of other CsA-associated toxicities (hypertension, hyperuricemia, tremor, hirsutism and edema) was observed.
Frequently reported TEAEs included dose/concentration-related laboratory abnormalities known to be associated with sirolimus.
The risks associated with maintenance Rapamune as base therapy included an increased incidence of associated adverse events such as thrombocytopenia, hypokalemia, elevated liver function tests, dyslipoproteinemia, poor wound healing and increased acute rejection rates post CsA withdrawal.

[9] OPTN data on kidney transplant recipient ethnicity reports 22.5% African Americans and 11.4% Hispanics. (1996 to 2001)

Renal allograft function slowly and progressively deteriorates with the chronic use of calcineurin inhibitors and we would expect that more than half of these transplants will fail within a decade. The impact of the CsA withdrawal and sirolimus maintenance concentration controlled regimen on long-term outcomes is yet to be determined. However, three years data continues to appear promising.

5.6. Approvability:

We have completed the review of the new proposed indication for Rapamune® as a maintenance regimen (RMR) following cyclosporine withdrawal in renal transplantation and have concluded that adequate information has been presented to demonstrate that the proposed indication is safe and effective for use as recommended in the agreed labeling text. This review included a Rapamune® 3-year safety update on study 0468H1-310-GL and the information provided suggests that the proposed indication has the potential to improve the care of renal transplant patients. It also provides to the transplant professionals with an alternative immunosuppressive regimen with potential benefits on long-term renal function.

In conclusion, we agree with the applicant that the combination of sirolimus plus CsA, and steroids early after transplantation followed by the elimination of CsA in conjunction with concentration-controlled sirolimus maintenance therapy is a safe and effective alternative to long-term CsA-based immunosuppression and may benefit a large proportion of the renal transplant population, namely those at low to moderate risk for rejection. The new proposed applications may be approved.

6. BACKGROUND

The FDA first approved the oral solution formulation of Rapamune® on September 15, 1999 (NDA 21-083). In August 25, 2000 the 1mg tablet (NDA 21-110) and recently in August 22, 2002 the 2mg tablet were approved.
The approved package insert recommends the use of this product in combination with cyclosporine and corticosteroids for the prophylaxis of organ rejection in patients receiving renal allografts. The basis of the initial 1999 approval of Rapamune® (sirolimus) included studies 301 and 302 (randomized, double-blind, phase III studies) comparing Rapamune®, 2 mg and 5 mg, to azathioprine or placebo respectively. Both studies demonstrated the non-inferiority of Rapamune® with respect to 12-month patient and graft survival, and a significant reduction in the incidence of rejection at 6 months. Despite a lower rate of acute rejection at 6 months post-transplantation, renal function, as measured by calculated glomerular filtration rate, was decreased at 12 months in the sirolimus treatment groups compared to controls.

The mean and median whole blood cyclosporine (CsA) concentrations levels remained at or above the upper limit of the specified target concentration ranges during these studies. Therefore, a phase IV commitment was made to evaluate the optimum therapeutic range for sirolimus and the value of reduced cyclosporine concentrations in combination with sirolimus. The Applicant also agreed to report long term follow-up safety and efficacy data from studies 301 and 302. It was requested that data on GFR and serum creatinine be included in an intent to treat analysis (ITT) (See action item # 3 of the February 08, 2002 FDA-approvable letter)

In April 2001 Wyeth Pharmaceuticals Inc. submitted supplemental applications containing studies protocols 212 and 310 (Cyclosporine elimination clinical studies, see table 6.1). This supplemental new drug application provides for the use of Rapamune ® (sirolimus) Oral Solution and Tablets within an immunosuppressive regimen that would allow for the elimination of cyclosporine 2 to 4 months after renal transplantation.

These studies evaluate the Rapamune-cyclosporine combination versus a cyclosporine-withdrawal arm. In this arm, cyclosporine is eliminated from the immunosuppressive regimen at 2-4 months post-transplantation, and Rapamune® dose is increased and adjusted to target trough sirolimus concentrations of 10 to 20 ng/ml for study 212 and 20-30 ng/ml for study 310 (by Immunoassay) during the first 12 months after CsA withdrawal.
Pivotal study 310 was an open label, non-IND study conducted in Europe, Canada and Australia with randomization at month 3 post-transplant. Study 310 excluded high-risk transplant recipients based on protocol specified exclusion criteria: Banff Grade III acute rejection episode or vascular rejection 4 weeks before random assignment, dialysis dependency, serum creatinine > 400 µmol/L, or inadequate renal function (in the opinion of the investigator) to support CsA elimination.

Study 212 was a phase II, an open-label, pilot study conducted in the US and Europe with randomization done at an earlier time than in study 310 i.e. at days 2 to 7 post-transplant. This study was completed in December 2000 and included 47/246 (19.1%) African Americans which under represents this population as well as other sub-populations[10]

[10] OPTN data on kidney transplant recipient ethnicity reports 22.5% African Americans and 11.4% Hispanics. (1996 to 2001)

Table 6.1

Study	Primary endpoint	Patients enrolled	Time of Rando-mization	Patients non-rando-mized	Patients rando-mized	Time of evaluation	Groups (No. patients)
310 *	Graft survival at 12 months	525	12±2 wks Post-op	95	430	24 mo.	Group A[2] 215 Group B[3] 215
212 **	Graft function at 6 months	246	1-7 days Post-op	49	197	12 mo.	Group A[2] 97 Group B[3] 100

*** CsA was tapered at month 3 and completely withdrawal at month 4 posttransplantation.**
**** CsA was tapered at month 2 and completely withdrawal at month 3 posttransplantation.**
[2] This group received sirolimus (SRL) plus CsA and corticosteroids. We will refer to this group also as SRL + CsA group or Group A
[3] This group withdrawal CsA at 3 or 4 months posttransplantation. We will refer to this group also as SRL group, CsA withdrawal group, or group B

The January 24, 2002-ACM members addressed the supplemental NDA and the need to determine the optimal sirolimus dose and method of therapeutic drug monitoring (TDM) as well as to identify the renal transplant population who would most benefit from using this concentration-controlled sirolimus and early cyclosporine elimination regimen.

After the final review of the supplemental application, the FDA issued an approvable letter on February 08, 2002. In this letter, the sponsor was asked to confirm the safety and efficacy of the proposed regimen and to complete all the post-marketing commitments established in the September15, 1999-approval letter for Rapamune® oral solution.
A pre-submission meeting was held on 29 Jul 2002 to review the proposed content and format of Wyeth's planned response to the 08 Feb 2002 approvable letter for the CsA-withdrawal indication.
FDA noted that it is customary for a response to an approvable letter to be complete. However, because studies 0468H1-316-GL (renal conversion study) and 0468H1-101164-US (high-risk study) will not be complete for a few years, Wyeth should provide a justification of the appropriateness to resubmit now, rather than await the completion of these studies. In addition, the FDA suggested several other analyses that should be included in the response.
The sponsor is presently re-submitting the proposed indication for Rapamune® as a maintenance therapy following early cyclosporine withdrawal (NDA 21-083/S-006 and NDA 21-110/S-004).

Addendum: ***This review includes a 3-year safety update on study 0468H1-310-GL that was submitted to the agency as a major amendment on January 31, 2003. The clinical data cutoff was 15 June 2002 for the 36-month data and 07 November 2002 for the cumulative data.***

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[2] This group received sirolimus (SRL) plus CsA and corticosteroids. We will refer to this group also as SRL + CsA group or Group A
[3] This group withdrawal CsA at 3 or 4 months posttransplantation. We will refer to this group also as SRL group , CsA withdrawal group, or group B

7. WYETH'S RESPONSE TO THE FEBRUARY 08, 2002 FDA -APPROVABLE LETTER

FDA acknowledged to receipt on October 15, 2002, the October 11, 2002 resubmission from Wyeth for the supplemental new drug applications for Rapamune® (sirolimus) Oral Solution and Tablets. The resubmission was considered complete, class 2 response to our February 8, 2002 action letter. Therefore, the user fee goal date is April 15, 2003.

On January 31, 2003 the applicant submitted a major clinical amendment. The amendment includes a safety summary (not a full clinical study report) with new information regarding 3-year data from study 310. The main purpose on this amendment is to include the 3-year data in the package insert at the time of approval. The applicant understands that administratively, it will add a potential 3-month extension to the review clock.

FDA Approvable Letter

1. Conduct an intent-to-treat analysis of safety, acute rejection, patient and graft survival, and the change in renal function over time up to 24 months post-transplantation in Study 310, which would demonstrate sustained improvement in renal function after withdrawal of cyclosporine.
This analysis should include measurement of renal function at 6, 12, 18 and 24 months post-transplantation, in all subjects randomized, whether or not they continued on study drug. It is recommended that such analyses include a slope intercept analysis of serum creatinine clearance over time.

Data from studies 310 and 212 at 24 months post-transplantation were submitted, ITT analyses were included. The incidence of rejection after CsA withdrawal is analyzed.

2. Address the impact of lost patients including disproportionate discontinuation and dropout in the two arms of the studies on the conclusions that may be made regarding the safety of the two regimens.
The sponsor submitted the discontinued patient analyses on studies 310 and 212.and concludes that lost patients or discontinued patients have not introduced bias that could impact on the safety conclusions from these studies

3. Complete your postmarketing commitment to provide long-term information from studies 301 and 302, including intent-to-treat information on renal function, whether or not patients continued on study drug. The 24-month reports submitted for these studies have only included on-therapy analyses of renal function and therefore do not meet this postmarketing commitment. Include a slope intercept analysis of serum creatinine clearance as well.
The intent-to-treat analyses from studies 301 and 302 at 24 months and 36 months following transplantation, respectively, indicate that renal function deteriorated among patients receiving the combination of CsA and sirolimus with increasing time on therapy. Findings were more pronounced, for patients receiving the 5-mg/day dose of sirolimus than for those receiving the 2-mg/day dose of sirolimus. Slope analysis of changes in 1/serum creatinine and Nankivell GFR over time, renal function also showed evidence of deterioration among patients in the

azathioprine and placebo comparator cohorts of these studies, although at slower rates than those noted in the sirolimus cohorts, and particularly at the 5-mg/day dose.

[redacted]

6. Define a therapeutic concentration range for sirolimus therapeutic drug monitoring in renal transplant patients whose cyclosporine has been eliminated by providing data and analyses that support this range and identifies the efficacious and maximum tolerated (safe) concentration.

The maximum tolerated concentration range for sirolimus-based maintenance therapy was previously explored in two phase 2 studies. The design of study 310 incorporated this information and prospectively demonstrated that a sirolimus concentration range of 15 to 30 ng/mL (12 to 24 ng/mL by chromatographic methods) is safe and effective when eliminating CsA 2 to 4 months posttransplantation.

These observations were supported by study 212. Although the sirolimus target ranges varied in this study, the observed sirolimus trough concentrations were similar to those observed in study 310, further supporting the recommended range.

8. POST-MARKETING COMMITMENTS ESTABLISHED IN SEPTEMBER15, 1999-APPROVAL LETTER THE FOR RAPAMUNE® ORAL SOLUTION.

Background:
Studies 301 and 302 showed decreased calculated GFR at 12 months in the sirolimus treatment groups compared to controls. In these studies the mean and median whole blood cyclosporine (CsA) concentrations levels remained at the upper limit or above of the specified target concentration ranges. As a result of this observation, a phase IV commitment was to evaluate the optimum therapeutic range for sirolimus and the value of reduced cyclosporine concentrations in combination with sirolimus. The applicant also agreed to report long term follow-up safety and efficacy data from studies 301 and 302. It was requested that data on GFR and serum creatinine be included in an intent to treat analysis (ITT)

Specific FDA Requests:

[ ]

9. FDA REQUESTS AT THE PRE-SUBMISSION MEETING ON JULY 29, 2002

Specific FDA Requests:

- ***To analyze serum creatinine and glomerular filtration rates (GFR) for Studies 310 and 301 stratified by rejector versus non-rejector.***
- ***Consider the timing of cyclosporine (CsA) withdrawal. It would be useful to determine which patients experienced an acute rejection while on the combination of sirolimus and CsA (this population may have differed between studies 301 and 310). Wyeth agreed to review the data for studies 301 and 302 and separate out those patients who could be considered low- and high-risk as well as stratified by rejector status.***

Pre-NDA meeting action items, July 29, 2002:

Action Item # 1: ***Wyeth's justification for not waiting until Studies 316 and 101164 are completed***
Action Item # 2: ***Rationale for Wyeth's proposed TDM scheme***
Action Item # 3: ***Analyses on relevant studies stratified by patients' rejector status***
Action Item # 4: ***Analyses on high-risk patients stratified by rejector status: S-301 and S-302***
Action Item # 5: ***Patient information from Study 310 regarding discontinuations***

10. ACTION ITEMS AND REVIEWED ANALYSES

The table below summarizes our approach for the review process.

February 08, 2002 FDA-approvable letter (FDA / Applicant agreements)	*Reviewed Analyses*
1.Conduct an intent-to-treat analysis of safety, acute rejection, patient and graft survival, and the change in renal function over time up to 24 months post-transplantation in Study 310, which would demonstrate sustained improvement in renal function after withdrawal of cyclosporine. This analysis should include measurement of renal function at 6, 12, 18 and 24 months post-transplantation, in all subjects randomized, whether or not they continued on study drug. It is recommended that such analyses include a slope intercept analysis of serum creatinine clearance over time.	ITT analysis on: • Safety • Acute rejection • Patient and graft survival • Renal function over time • SCr and GFR slope intercept analysis
2. Address the impact of lost patients including disproportionate discontinuation and dropout in the two arms of the studies on the conclusions that may be made regarding the safety of the two regimens.	Discontinuations and drop outs Studies 310 and 212
3. Complete your postmarketing commitment to provide long-term information from studies 301 and 302, including intent-to-treat information on renal function, whether or not patients continued on study drug. The 24-month reports submitted for these studies have only included on-therapy analyses of renal function and therefore do not meet this postmarketing commitment. Include a slope intercept analysis of serum creatinine clearance as well.	Long term data studies 301 and 302 • ITT analysis on renal function, SCr and GFR slope intercept analysis.
[redacted]	[redacted]
6. Define a therapeutic concentration range for sirolimus therapeutic drug monitoring in renal transplant patients whose cyclosporine has been eliminated by providing data and analyses that support this range and identifies the efficacious and maximum tolerated (safe) concentration.	• Therapeutic concentration ranges • Efficacious and Maximum safe concentration. (Office of Clinical Pharmacology and Biopharmaceutics Review)

Agency requests at the pre-submission meeting on 29 Jul 2002, Action items and reviewed analyses
• *Wyeth's justification for not waiting until Studies 316 and 101164 are completed*
• *Rationale for Wyeth's proposed TDM scheme*
• *Analyses on relevant studies stratified by patients' rejector status*
• *Analyses on high-risk patients stratified by rejector status: S-301 and S-302*
• *Patient information from Study 310 regarding discontinuations*

Reviewer's comment: *The resubmission from Wyeth for the supplemental new drug applications for Rapamune® was considered complete. A major amendment was submitted on January 31, 2003, which provides for a 3-year safety summary on study 310. This amendment is also included in this review.*

11. EFFICACY AND SAFETY ANALYSES FOR STUDY 310 AND 212

Action item #1 from the February 08, 2002 FDA-approvable letter:
"***Conduct an intent-to-treat analysis of safety, acute rejection, patient and graft survival, and the change in renal function over time up to 24 months post-transplantation in Study 310, which would demonstrate sustained improvement in renal function after withdrawal of cyclosporine. This analysis should include measurement of renal function at 6, 12, 18, and 24 months post-transplantation, in all subjects randomized, whether or not they continued on study drug. It is recommended that such analyses include a slope intercept analysis of serum creatinine clearance over time.***"

To address this requirement, the sponsor presented data from cyclosporine withdrawal studies **310** and **212.**

S-310 primary endpoint was assessing equivalence in the rates of functional graft survival at 12 months. This study enrolled 525 patients from which 95 (18%) were discontinued or excluded from randomization during the first 3 months on CsA + SRL treatment. The review of this study includes a 3-year safety update submitted to the agency as a major clinical amendment on January 31, 2003. It will also provide information on cumulative data from June 15, 2002 to November 7, 2002.

S-212 primary endpoint was to assess graft function. Efficacy was assessed by the comparison of serum creatinine levels between patients in group A[11] and group B[12], who were rejection-free and continuing to receive study drug six months after administration of the first dose (the valid-for-efficacy [VFE] sub-population). Table 11.1 provides with a summary of relevant similarities and differences between studies 310 and 212.

Table 11-1 SUMMARY OF STUDIES 310 AND 212

Study	Primary endpoint	Patients enrolled	Time of Randomization	Patients non-randomized	Patients randomized	Time of evaluation	Randomized Groups	Time for CsA withdrawal	SRL and CsA Doses
310 a.	Graft survival at 12 months	525	12±2 wks Post-op	95	430	36 mo.	Group A[1] 215	no	2mg-fixed-dose SRL and CsA 75-200 ng/mL.
							Group B[2] 215	3-4th month post-op	CsA elimination and concentration-controlled sirolimus (20-30ng/ml-for 12 months
212 a.	Graft function at 6 months	246	1-7 days Post-op	49	197	12 mo.	Group A[1] 97	no	2mg-fixed-dose SRL and CsA 150-250 ng/mL.
							Group B[2] 100	2-3 rd month post-op	CsA elimination and concentration-controlled SRL (10-20 ng/ml-for 12 months

a. Open-label, multicenter, randomized, controlled trials

[11] This group received sirolimus plus CsA and corticosteroids. We will refer to this group also as SRL + CsA group or Group A

[12] This group withdrawal CsA at 3 or 4 months posttransplantation. We will refer to this group also as SRL group , CsA withdrawal group, or group B

Reviewer's Comment: ***There are similarities and differences between studies 310 and 212. The design in both studies is open label and randomized concentration controlled. The main differences are the time of randomization, target though blood levels and follow-up time. Therefore, the data analysis for both studies will be integrated together whenever possible.***
This part of the review is divided in two section:

- **EFFICACY RESULTS STUDY 310 AND 212,** ***and***
- **SAFETY RESULTS STUDIES 310 AND 212**

Both section include data from a 3-year safety update on study 0468H1-310-GL that was submitted to the agency as a major amendment on January 31, 2003.

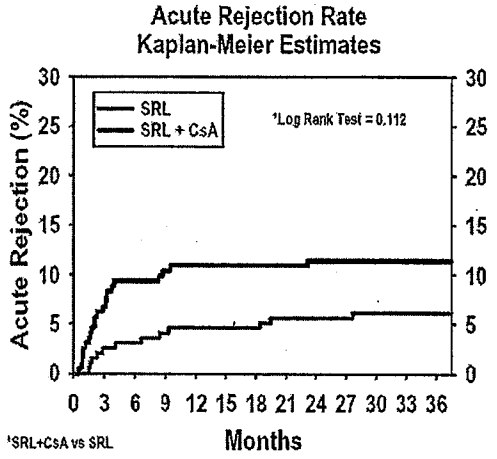
11.1 EFFICACY RESULTS STUDY 310 AND 212

S-310: The percentage of patients on therapy at 24 months were similar between arms (65.5% and 66.5% in groups A and B, respectively). 24-months ITT efficacy analyses were performed on all randomized patients.

11.1.1 First Biopsy Confirmed Acute Rejection (BCAR)

S-310: Acute Rejection 24-months ITT Analysis:

Fig 11.1.1-a TIME TO FIRST ACUTE ALLOGRAFT REJECTION POSTRANDOMIZATION (STUDY 310) From **Fig 5.2B**, page 18, 3yrs safety update S-310.



Most of the acute rejections post-randomization occurred within the following 3 months. The curves in the Kaplan-Meier ITT analysis plot diverge after randomization, with an increased number of AR episodes in the group B (CsA withdrawal). At 12 months post randomization first BCAR rate was significantly higher in group B (9.8%) vs group A (4.2%), p = 0.036. In the following 24 months additional AR episodes were observed in both groups. At the end of 36 months follow up the first BCAR rate was still higher in group B (10.2%) vs. group A (5.6%) although not statistically significant (p= 0.107)

Similarly, in **S-212** first BCAR proportion rates were numerically higher in group B at 6 and 12-month follow-up periods.

First and Second BCAR episode after randomization:

During the first three months post-transplantation (pre-randomization period) in **S-310**, 42/525 patients experience BCAR and they were evenly randomized. Of those, 5/20 (25%) in group A and 4/22 (18.2%) in group B experienced a second BCAR episode after randomization. This difference was not statistically significant.

Table11.1.1-1. RATES OF FIRST BCAR STUDIES 310 AND 212, ITT ANALYSIS POSTRANDOMIZATION.
Modified from table 5.2A, page 16, 3yrs S-310 safety update.

Postrandomization Periods	**Group A SRL + CsA**	**Group B SRL**	**A – B (95% CI)**	**A vs B* p-Value**
Study 310 (24 months)**	5.1% (11/215)	**9.8%** (21/215)	-4.7% (-9.6, 0.3)	0.097
Study 310 (36 months)	5.6% (12/215)	**10.2% (22/215)**	-4.7(-9.7, 0.4)	0.107
Study 310 (>36 months / cumulative)**	6% 13/215	**10.2%,** 22/215	-4.2 (-9.3, 1.0)	0.157
Study 212 (12 months) ***	18.6% (18/97)	**22%** (22/100)	3.4 (-7.8, 14.7)	0.598

ITT analysis: Includes both on therapy after randomization and follow-up after discontinuation periods.
*Fisher's Exact test
** Postrandomization to 12 , 24 and 36 months **(CsA was tapered at month 3±2wks and completely withdrawal at month 4 posttransplantation.**
*** Patients were randomized during the first 7 days posttransplantation **(CsA was tapered at month 2 and completely withdrawal at month 3 posttransplantation).**

Table 11.1.1- 2. POSTRANDOMIZATION FIRST BIOPSY-CONFIRMED ACUTE REJECTION BY GRADE STUDY310, 36 MONTHS FOLLOW UP ON THERAPY ANALYSIS.
Modified from table 5.2C, page 17, 3yrs safety update.

Grade of Rejection	**Group A SRL + CsA**	**Group B SRL**
Mild	6/7**a** (85.7)	14/21 (66.7)
Moderate (2a)	1/7 (14.3)	6/21 (28.6)
Moderate (2b)	0	1/21 (4.8)
Severe	0	0
Total: Rejection on therapy	7	21

a: Denominator = total number of first BCAR in patients on therapy.
Post-randomization, 112/215 patients (52%) from group A and 134/215 (62%) from group B were on treatment by 36 months.

Reviewer's Comment: *Post- CsA elimination, group B presented an increased rate of BCAR in both studies 310 and 212. The BCAR rate persisted numerically higher in the CsA elimination group at 12, 24, 36 in both S-212 and S-310 (table 1). Most of the BCAR episodes were mild and the rate differences between groups A and B were not*

statistically significant. However, patients that remained on therapy presented higher grades of rejection in group B versus group A (table 2)
Severe acute rejections did not occur following randomization in either group A or B in both studies 310 and 212.

In S-310 prerandomization phase, nine (9) patients presented severe BCAR . Three of those were randomized (one to group A and two to group B. Due to the limited data(only 3 patients/525), a previous severe BCAR might preclude the use of the proposed regimen in this subgroup of patients, even if they recover stable renal function. Severe acute rejection during the early post transplant period may indicate high immunological risk per se.

It is well known that AR has a deleterious effect on renal function and graft survival. Numerically higher BCAR rates were observed in group B and these were not associated with a detectable deleterious effect on graft function or graft survival at 12 and 36 months (Studies 212 and 310, respectively). On the contrary graft function and graft survival favors group B.

11.1.2. First BCAR Analysis by Sub-population

<u>Reviewer's Comment:</u> Patients that experience acute rejection in S-310 were analyzed by sex, living vs cadaver donor, primary vs secondary graft, presence or absence of delayed graft function, age of donor, donor ischemia time, patient age, and use of antithymocyte globulin (ATG) or murine monoclonal antibody OKT3. Acute rejection rate differences were not statistically significant. The number of patients included in the subsets were small to draw definitive conclusions.

Analyses by Race at 12 months study 212:

Table 11.1.2-1. NUMBER (%) OF PATIENTS WITH BCAR BY RACE (BLACK, NONBLACK) AT 12 MONTHS AFTER TRANSPLANT: ITT POPULATION: STUDY 212

Month 12 (≤379 days)	Group A SRL + CsA N=97	Group B SRL n=100	Fisher's Exact p-value Group A vs Group B
Black, n[a] (%)	6/18[a] **(33.3)**	5/15 **(33.3)**	1.000
Non-black, n[a] (%)	12/79 **(15.2)**	17/85 **(20.0)**	0.540
Fisher's Exact p-value	0.095	0.310	

a: The numerator is the number of patients with acute rejection; the denominator is the number of patients of that race.

<u>Reviewer's Comment:</u> Higher rates of BCAR were observed in black patients compared with non black patients in both groups A and B. The differences observed in groups A versus B were not statistically significant for both black and non-black patients. The small number of black subjects included in this study limit the strength of the conclusions that may be drawn from these analyses.

11.1.2.2. Analysis by the degree of HLA mismatch:

Table 11.1.2.2-1. NUMBER (%) OF PATIENTS WITH >3 HLA MISMATCHES AND BCAR ITT POPULATION b STUDIES 212 AND 310.

>3 HLA mismatches, n[a] (%)	Group A SRL + CsA	Group B SRL	Fisher's Exact p-value Group A vs Group B
S-310 Pre randomization	7/67 (10.4%)	10/72 (13.9%)	0.610
S-310 Post randomization (24 months)	2/67 (3.0%)	11/72 **(15.3%)**	**0.018***
S-212 (12 months)	7/37 (18.9)	11/45 (24.4)	0.601

a: The numerator is the number of patients with acute rejection; the denominator is the number of patients with > 3 HLA mismatches.
b: Includes both on therapy after randomization and follow up after discontinuation periods.
Modified from table 9.42.2.4A, protocol 048E1-212 page 100and 5.1.B C, pages 11 and 12, 3yrs Rampamune®safety update.

Table 11.1.2.2-2. PATIENTS SURVIVAL BY DEGREE OF HLA MISMATCH STUDY 310.

HLA mismatches, n[a] (%)	Group A SRL + CsA	Group B SRL	Difference (95%CIs)
≤ 3	88.5	93	**-4.4(-11.1, 2.2)**
>3	88.1	95.4	**-6.4(-15.8, 3.0)**

Table 11.1.2.2-3. GRAFT SURVIVAL BY DEGREE OF HLA MISMATCH STUDY 310.

HLA mismatches, n[a] (%)	Group A SRL + CsA	Group B SRL	Difference (95%CIs)
≤ 3	85.8	89.4	
>3	83.4	94.4	

***Reviewer's Comment:** Patients with > 3 HLA mismatches in the CsA withdrawal arm had numerically or significantly higher acute rejection rates in both S-310 and S-212. However, patient and graft survival were not affected in the CsA withdrawal arm by the higher rate of BCAR in this sub-population. Patient and graft survival were superior in the CsA withdrawal arm regardless of the degree of HLA mismatch.*

11.1.3. Patient and Graft Survival ITT Population

Patient survival was similar in both S-310 (95.3% vs. 94.0%) and S-212 (96.0% vs. 96.9%) and across arms (group A versus B, respectively). Table 6 shows patient survival and cause for death in each group in study 310 and 212.

Table 11.1.3-1. PATIENT SURVIVAL AND CAUSES FOR DEATH S-310 AND S-212 ITT ANALYSIS. (12 months and 24 months, respectively)

	Study 310			Study 212		
	Group A SRL + CsA (n = 215)	Group B SRL (n = 215)	Nonrandomized SRL + CsA (n = 95)	Group A SRL + CsA (n = 97)	Group B SRL (n = 100)	Nonrandomized SRL + CsA (n = 49)
Patient Survival	202 (94%)	205 (95%)	72 (76%)	94 (97%)	96 (96%)	44 (90%)
Deaths	11 (5%)	8 (4%)	18 (19%)	3 (3%)	4 (4%)	4 (8%)
			Cause for death			
Cardiovascular	4	5	9	2	3	3
Infection	5	3	5	1		1
Other	2		4		1	
Lost to follow-up	2 (1%)	2 (1%)	5 (5%)	0	0	1 (2%)

Modified from, **Overall long-term patient and graft survival, acute rejection, and serious adverse events summary, tables 2.3.1.B, 2.3.2A and 2.3.2B pages 45, 46 and 48, respectively.**

***Reviewer's Comment:** As expected cardiovascular events and infections were the primary reasons for death in each group. In S-310 and 212, the number of deaths in nonrandomized groups were greater than that in groups A and B. This observation agrees with the fact that the selection criteria for randomization was successful in excluding high risk patients. The difference between randomized groups was not significant.*

Table 11.1.3-2. GRAFT SURVIVAL* STUDIES 310 AND 212 ITT ANALYSIS.

Study	Nonrandomized Group C SRL + CsA	Group A SRL + CsA	Group B SRL	A-B % (95%CI)
S- 310 24 months	**49.5%** (47/95)	**91.2%** (196/215)	**93.5%** (201/215)	-2.3(-7.4, 2.7)
S- 310 36 months	**45.3%** 43/95	**85.1%** (183/215)	**91.2%** (196/215)	-6.0(-12.1, 0.0)
S- 310 Cumulative	**44.2%** 42/95	**81.4%** (175/215)	**89.8%** (193/215)	-8.4 (-15.0, -1.8)
Study 212 12 months	**77.6 %** (38/49)	**92.8%** (90/97)	**95%** (95/100)	-2.2 (-8.9, 4.5)

***Do not include deaths with functioning graft. Death with a functioning graft was scored as graft loss.** Modified from table 5.1.A and 5.1.B C, pages 11 and 12, 3yrs Rampamune® safety update and protocol 048E1-212 Table 9.4.2.4A , page 103.

Reviewer's Comment: ***Graft survival ITT population was similar between groups A and B in both studies 310 and 212 at 12 and 24 months, respectively. In S-310, the difference in graft survival has increased from 24 to 36 months (Table 3). This increased difference was mainly due to an increased number of graft losses in group A compared with group B.***

Table 11.1.3-3. GRAFT LOSS: NUMBER (%) OF PATIENTS, 24 AND 36 MONTHS, STUDIES 212 AND 310 RESPECTIVELY

	Study	Group A SRL + CsA	Group B SRL	Group C Non-randomized SRL + CsA
Graft Loss without deaths, n (%)	**310***	**15 (7.0)**	**7 (3.3)**	**34 (35.8)**
	212	4 (4.1)	1 (1.0)	6 (12.2)
Death with functioning graft	**310**	**10(4.7)**	**8 (3.7)**	**14 (14.7)**
	212	3 (3.1)	4 (4.0)	4 (8.2)

*Includes lost of follow-up patients

Reviewer's Comment: ***Non-randomized patients (group C) in S-310 and S-212 had higher rates of graft loss and death with functioning graft than groups A and B. Death with functioning graft was the most common etiology of graft loss in all groups.***
In S-310, graft loss (table 4) in group C was due to renal vascular thrombosis, prolonged acute tubular necrosis (ATN) and chronic dysfunction. Death with functioning graft was also higher in this group 14%, 4%, 3 % for groups C, A and B, respectively.
The group C higher graft loss rates confirms that criteria for randomization in S-310 and S-212 was capable to identify a high risk group of patients that would not be expected to benefit from the CsA elimination regimen.

11.1.4. REVIEWER'S SUMMARY AND CONCLUSION ON EFFICACY S-310 AND S-212:

Patient and Graft Survival:

- ***Patient survival was similar in both S-310 (95.3% vs. 94.0%) and S-212 (96.0% vs. 96.9%) and across treatment arms (group A versus B, respectively).***
- ***Data from S-310, 3-year safety update showed an increasing difference in graft survival across treatment favoring group B. According to protocol statistical parameters, graft survival in group B is not inferior compared to group A (A - B = -6.0%: 95% CI= -12.1 , 0.0)***

Acute Rejection:

- ***First BCAR was numerically higher in the cyclosporine withdrawal arm compared with the CsA + SRL group and severity of rejection was similar between two groups.***
- ***Including First or second acute rejection, also showed higher AR rates in the CsA withdrawal arm.***
- ***BCAR episodes were mild to moderate and the differences between groups A and B were not statistically significant. Severe acute rejections did not occur following randomization.***
- ***In general, after cyclosporine withdrawal (group B), there was a transient increase in the number of BCAR episodes. This increased rate of AR, although not statistically significant and mild to moderate in severity, is clinically relevant because it implies at least additional treatment with steroids. It is well known that AR is an important risk factor for chronic rejection. AR episodes occurring after 3 or 6 months confer the greatest risk for chronic rejection and late renal graft loss according to published data[13],[14]. However, at 12 and 36 month follow-up (studies 212 and 310, respectively), numerically higher rates of acute rejection in group B did not result in a significantly lower graft survival. On the contrary group B had numerically lower graft losses.***

Sub-populations:

- ***As expected, patients with higher degree of HLA mismatches had a higher rate of BCAR. In the pivotal S-310, patients with > 3 HLA mismatches presented significantly higher first BCAR rates in the CsA withdrawal arm (15.3%) compared with group A (3.0%), p = 0.018. It is well known that acute rejection has a negative impact on renal function and long term graft survival***

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[13] Humar A, Kerr S, Gillingham KJ, et al. Features of acute rejection that increase risk for chronic rejection. Transplantation 1999; 68: 1200–1203.

[14] Yvo w. J. Sijpkens, Ilias I. N. Doxiadis et al. Early versus late acute rejection episodes in renal transplantation Transplantation 2003; 75: 204–208.

Interestingly, patient and graft survival were not affected in the CsA withdrawal arm by the higher rate of first BCAR in this sub-population. Renal function was superior in the CsA withdrawal arm compared to the CsA + SRL group regardless of the degree of HLA mismatch. We agree with the applicant that this sub-population could also benefit from the CsA withdrawal and RMR. However, long term data on renal function, patient and graft survival at 5 years posttransplantation will further validate or dispprove these findings at 3 years.

- ***Study 310 was conducted outside of USA, It did not adequatelyrepresent all sub-populations. African American and Hispanic populations were underrepresented in the CsA elimination studies. Even though, S-212 had a better representation of the African American population (19% in group A and 15% in group B) we cannot recommend the CsA elimination regimen for these sub populations due to the limitations of such a small database. On the other hand we cannot exclude the possibility that that AA and Hispanic patients with a low immunologic risk[15] could be suitable candidates for CsA withdrawal and RMR.***

- ***S-212: Caucasian patients experienced higher rates of rejection in the cyclosporine withdrawal arm, 20% versus 15.2% groups B and A respectively. African American patients presented numerically higher rates of BCAR compared with Caucasians but there was no difference between treatment arms among African Americans (33.3% BCAR rates in both groups A and B).***

[15] Demonstrated by lack of BCAR episodes during the first three months posttransplantation, for example.

11.2. SAFETY RESULTS STUDIES 310 AND 212

11.2.1. Patient Discontinuation Rates:

Adverse reaction and unsatisfactory response-efficacy were the most common causes of discontinuation accounting for 75% and 85% of the total patient discontinuation in **S-212** and **S-310**, respectively.

Reviewer's Comment: ***The causes for discontinuation and discontinuation rates were similar in groups A and B in both S-310 and S-212, post-randomization. In S-310, unsatisfactory response to treatment and AE rates were similar across groups and no imbalances in discontinuation rates were observed across randomized groups.***
A more detailed analysis of the number of patients who discontinued from sirolimus therapy along with the causes of discontinuation are discussed in this review under the section:

- **ANALYSIS ON DISCONTINUED PATIENTS : On-Therapy, Completers, and LOCF Analyses.**

11.2.2. Adverse Events:

ITT analysis was only available for Severe and Life-threatening Events. For all other Treatment-emergent Adverse Events (TEAEs), the applicant presented on therapy analyses.

11.2.3. Treatment-emergent Adverse Events (TEAEs) Studies 310 and 212:

The TEAEs profile post-randomization was similar to that reported in previous studies of patients on sirolimus[16]. This profile consisted of a group of adverse events significantly higher in the CsA elimination, group B compared with group A and they are considered as concentration related adverse events since they become apparent in the group of patient receiving higher sirolimus dose.

Statistically significant differences in TEAEs from studies 310 and 212 are summarized in tables **11.2.3-1, 11.2.3-2.** and **11.2.3-3.**.

Reviewer's Comment: ***Hypercholesterolemia and hypertriglyceridemia, reported as adverse events, were higher in group B versus group A in both S-310 and S-212. This difference was not statistically significant, probably due to the fact that the majority of these patients are on therapy for hyperlipidemia which was tailored to the specific patient's requirement. This type of intervention decreases the difference between groups. This observation is consistent with the pre-randomization TEAEs profile in which relevant adverse events were hypercholesterolemia, hypertriglyceridemia (before the anti hyperlipidemic therapy was fully adjusted to patient-specific requirements).***

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[16] Kahan BD, Rapamune Study Group. The Lancet 356 (9225):94-202 (Study 301)
The type and the incidence of events were similar to those reported in previous phase 3 studies (0468E1-301-US and 0468E1-302-GL).

Table 11.2.3-1. TREATMENT-EMERGENT ADVERSE EVENT RATES POST-RANDOMIZATION, STUDY 310

TEAE	Group A SRL + CsA n=215	Group B SRL n=215	
Thrombocytopenia a.	4.7%	**12.1%**	p = 0.008
Hypokalemia	2.3%	**9.8%**	p = 0.002
Abnormal LFT's	3.7%	**9.8%**	p = 0.020
SGOT/AST	4.7%	**15.3%**	p < 0.001
Abnormal healing	0.9%	**4.7%**	P= 0.036
Ileus	0%	**2.8%**	P= 0.030

a. No clinical bleeding

Table 11.2.3-2. TREATMENT-EMERGENT ADVERSE EVENT RATES POST-RANDOMIZATION, STUDY 310

TEAE	Group A SRL + CsA n=215	Group B SRL n=215	
CsA toxicity	**8.8%**	2.8%	p = 0.012
Hypertension	**21.4%**	8.8%	p < 0.001
Hyperuricemia	**14.4%**	5.6%	p = 0.003
Creatinine increased	**28.8%**	17.7%	p = 0.008
Abnormal kidney function	**13.5**	6.5%	p = 0.023
Toxic nephropathy	**4.2%**	0.5%	p = 0.020
Edema	**8.4%**	2.8%	p = 0.019
Cataract	**6.5%**	1.9%	p = 0.028
Malignancies a.	**9.8%**	4.2%	p = 0.036

All of these findings with the exception of cataracts, would be expected based on the established clinical profile of CsA. Patients were not systematically screened for cataracts and, therefore, the finding regarding cataracts requires further confirmation

a. Please see section on: **Malignancy Related TEAE Study 310, 36 month analysis** and table 7.

Table 11.2.3-3. TREATMENT-EMERGENT ADVERSE EVENT RATES POSTRANDOMIZATION, STUDY 212

TEAEs Rates, Study 212	Group A SRL + CsA n=97	Group B SRL n=99	
Events statistically significantly more common in group A versus group B			
hypertension	**46.4%**	30.3%	p = 0.027
dyspnea	**20.6%**	9.1%	p = 0.027
edema	**14.4%**	3.0	p = 0.005
hypervolemia	**12.4%**	4.0%	p = 0.039
hypomagnesemia	**12.4%**	4.0%	p = 0.039
Events statistically significantly higher in group B versus group A			
thrombocytopenia	14.4%,	**28.3%**	p = 0.023
diarrhea	11.3%	**25.3%**	p = 0.016
hypokalemia	13.4%,	**25.3%**	p = 0.046
abnormal liver function test	7.2%,	**17.2%**	p = 0.048
atrial fibrillation	1.0%,	**8.1%**	p = 0.035

Reviewer's Comment: ***In both CsA withdrawal studies (S-310 and S-212), continued administration of CsA in group A (CsA + SRL) was associated with a significantly higher frequency of known CsA-related toxicity(Hypertension, hyperuricemia, nephrotoxicity etc.). On the other hand patients randomized to the CsA withdrawal arm, and thus exposed to high sirolimus concentrations, presented significantly higher rates of thrombocytopenia, hypokalemia, diarrhea, abnormal liver function tests and abnormal wound healing.***
The increased difference in thrombocytopenia was not associated with increase in clinical bleeding, Hypokalemia responded adequately to medical management.
Abnormal LFT's lead to discontinuation in 6 patient in group B S-310.
All patients in S-212 and 310 were receiving steroids as well as SRL. For this reason, the relative contribution of each drug to the abnormal wound healing in group B is difficult to evaluate. However, we know that this adverse event could have catastrophic consequences when SRL and steroids are used concomitantly, e.g. anastomosis disruption. For further detail, please see:

- **SAFETY RESULTS STUDIES 310 AND 212: Laboratory Tests** ***and***
- **ANALYSIS ON DISCONTINUED PATIENTS : On-Therapy, Completers, and LOCF Analyses for Selected Laboratory Parameters** ***sections.***

11.2.4. ITT Analysis of Severe and Life-Threatening Adverse Events S-310:

Abnormal kidney function incidence was significantly higher group A (5.1% vs. 0.9%, p = 0.021 groups A and B, respectively). Severe and life-threatening infection rate was the same in both groups (14.9%). The overall incidences of severe and life-threatening treatment-emergent events excluding infections was similar across treatment arms (36.6% vs.34.9% group A vs group B, respectively (p = 0.683).

Reviewer's Comment: ***A significantly higher incidence of abnormal kidney function was observed in the CsA + SRL arm, group B.***

11.2.5. TEAE Related to Malignancy Study 310, 36 month analysis:

The overall malignancy rate was numerically lower in the CsA elimination group (5.6% versus 11.2%, respectively, p = 0.054).
Skin carcinoma was the most frequently reported malignancy. In group A, fourteen- (14) cases were reported and 8 cases in group B (5/8 of the cases in group B occurred 3.1 to 31.5 months after the patient's withdrawal from group B).
Single cases of other type of cancer were reported for group A (Prostatic carcinoma, Glioma, Oropharynx cancer, and Acute leukemia) and for group B (Cervix carcinoma, and Microcarcinoma of the thyroid). Two cases of Renal carcinoma (Both in group A) and three cases of lung carcinoma (two in group A and one in the non-randomized group)

Table 11.2.5-1. MOST FREQUENT MALIGNANCIES REPORTED. STUDY 310 a,b. **(36 MONTHS)**
Modified from table 6.3A 3yrs safety update, page 34.

Malignancies	Group A SRL + CsA (215)	Group B SRL (215)	Group C SRL + CsA Non-randomized (95)
Skin carcinoma, Total No (%)	14 (6.5)	8 (3.7)	4 (4.2)
Any Squamous Cell c. (%)	1.9	**2.3**	1.1
Any Basal Cell c.	**4.7**	2.3	3.2
Melanoma	0.5	0	0
Miscellaneous / Not Specified	0.9	0	1.1
Lymphoma/lymphoproliferative disease	3 (1.4)	1 (0.5)	1 (1.1)
Other Malignancy	**3.3%**	**1.4%**	**1.1%**

a. All patient received corticosteroids
b. Includes discontinued patients
c. Patients may be counted in more than one category

Reviewer's comment: ***Patients in group B developed less skin cancers. However, It would be premature to attribute the difference in reported malignancies to an anti-proliferative effect from higher concentrations of sirolimus. Basal cell carcinoma was the most frequently reported malignancy in group A. This malignancy represents the least aggressive of all skin cancers and it is successfully treated. On the other hand Squamous cell carcinoma is more aggressive because of its ability to metastasize. Therefore, differences in malignancy behavior should be taken into consideration when attempting to interpret differences between treatment arms.***
Four cases of Lymphoma/lymphoproliferative disease were reported, three of them in group A.
Please see: **LONG-TERM INFORMATION FROM STUDIES 301 AND 302** ***under Malignancies.***

11.2.6. Deaths:

Table 11.2.6-1 DEATHS*

	Group A SRL + CsA	Group B SRL	Group C SRL + CsA
STUDY 310	11**	8	18
STUDY 212	3	4	4

*Excludes patients lost to follow-up.
** Number of deaths

Reviewer's Comment: ***Individual case reports were reviewed and no abnormal pattern was observed. In general, cardiovascular events, and infection were the most common causes of mortality in both S-310 and S-212, which are the main causes of death in the renal transplant population. In S-310, more number of deaths occurred in group A. Non-randomized patients (High-risk population) presented the highest number of deaths among all groups. (Please see:***

- **SAFETY AND EFFICACY ANALYSES FOR STUDY 310 AND 212", Table 6.**
- **PATIENT SURVIVAL AND CAUSES FOR DEATH S-310 AND S-212 ITT ANALYSIS (12 months and 24 months, respectively)** ***and***
- **LONG-TERM INFORMATION FROM STUDIES 301 AND 302 under Patient Survival and Causes for Death**

11.2.7. Analysis of TEAE Related to Infections.

S-310:

Post randomization on therapy analysis, 36 months follow up:

Herpes zoster infection rate, reported as TEAE, was significantly higher group A (6.5%) than in group B (0.9%), p = 0.004. Pneumonia rates were significantly higher in group B at 12 months. This rate was no longer significant at 36 months (14.4% versus 9.3%, group B versus group A, p = 0.135). The etiology of the pneumonia was not identified in 67 % of the cases (27 out of 41 cases in both groups). Deaths occurred in 9.7%, 2 cases in each group. Anti-infective therapy was effective in the remaining 37 cases.

Severe or life-threatening infections: In more than 2% range included infections in general, sepsis, pyelonephritis, urinary tract infection and pneumonia. Pneumonia as a life-threatening infection presented the highest rates (5.6% in group A and 3.7% in group B).

Study 212: The incidence of patients reporting 1 or more infection-related TEAE was similar in the 2 groups (68.0% and 67.7% in groups A and B, respectively). Fungal dermatitis rate was significantly higher in group B (6.1%) compared with group A (0%).

Reviewer's comments:

Culture, serology or biopsy was not required to document or include an event as a TEAE related to infection. Therefore, results regarding etiology, should be evaluated with caution.

No clinically significant imbalances were observed between arms regarding the rates of infections during the pre-randomization phase in S-310.

The type and number of infections were similar in both S-310 and S212 and across arms.

Excluding herpes zoster and Fungal dermatitis, there were no significant differences across arms in the rates of infections and severe life threatening infections by The COSTART system (body system or by type of infection in both S-310 and S-212. Higher rates in herpes zoster infection in group A, S-310 and fungal dermatitis in group B, S-212 were observed. However, the clinical impact of these differences is not a major concern. Please see: **LONG-TERM INFORMATION FROM STUDIES 301 AND 302** ***under Infections.***

11.2.8. Renal Function:

Reviewer's comments: The ITT and on-therapy analyses demonstrated better GFR among CsA withdrawn patients compared with patients who continued on CsA plus sirolimus combination (S-212 and S-310). We agree with the applicant that CsA

withdrawal, in the populations studied, is associated with superior renal function through 36 months posttransplantation compared with the patients that continue on CsA + SRL combination.
A detailed analysis on renal function is reviewed under the following sections:
- ***ITT RENAL FUNCTION DATA ANALYSIS ON STUDIES 310 AND 212 (Impact of cyclosporine-withdrawal on renal function) and***
- ***ITT ANALYSIS STUDIES 301 AND 302 (Long-term Renal Function, Change on Renal Function Over Time).***

11.2.9. Laboratory Tests

Hemoglobin: In both **S-310** and **S-212** and across arms, hemoglobin mean values increased after transplantation and reach values ≥ 120g/L at 6 months approximately. After randomization there were significantly lower mean hemoglobin values in group B during the first 12 months compared to group A. This observation reversed and by the end of the 24 months, slightly higher mean values were observed in group B.
In **S-212**, hemoglobin mean values were not statistically significantly different between treatment arms any time point.

White blood cell counts: In both **S-310** and **S-212,** mean WBC values remain stable and within acceptable range across treatment arms. All mean values were above 6,000 per mm3 during the follow-up period in both studies. During the first 12 months in S-310, the mean values for group B were lower than group A. After 12 months there was no difference between mean values.

Platelets: Mean values for platelet counts were between 200,000 to 230,000 / mm3 in both studies and across arms. From randomization through approximately month 18, mean values for group B were slightly, but significantly, lower than those for group A. The mean values were within acceptable range, and the differences between treatment arms are not clinically relevant.
There were no discontinuations for thrombocytopenia in either group at 24 or 36 months.

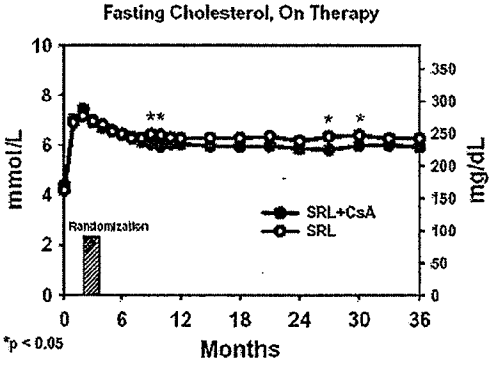
Reviewer's comment: ***Leukopenia, thrombocytopenia and anemia are dose-related toxicities recognized for sirolimus since its original NDA. In pivotal S-310, hematologic adverse events led to patient discontinuation in 5% and 3%, groups A and B, respectively. The mean values for hemoglobin, WBC and platelets over time are within acceptable range (on-therapy, completers, and LOCF analyses) and the differences across arms are clinically acceptable. The difference in platelet counts were not associated with any difference in clinical bleeding. Thrombocytopenia was not a cause for discontinuation.***

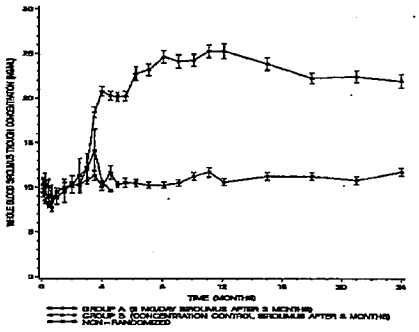
Serum Lipids:
The applicant presented on therapy, LOCF and completers analyses for serum lipids. The graphic representation of these analyses presented similar curves among them and across arms. Therefore, the conclusions drawn from the on therapy analysis are acceptable despite the patient discontinuations. These analyses were reviewed and evaluated

according to the classification defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines[17]

Reviewer's comment: In ***S-310, Serum cholesterol and triglycerides mean values rapidly increased during the pre-randomization period and peaked at month 2, while receiving SRL + CsA. After randomization, mean lipid values in both arms slightly decreased through month 9 and level up thereafter. However, they never returned to baseline or desirable level despite therapeutic intervention.***
The mean values were either numerically or significantly higher in group B and always remained in the high level range for cholesterol, and triglycerides. The LOCF analysis clearly showed these differences across arms. Sirolimus is associated with dyslipidemias and its concomitant use with CsA enhances this toxicity. Interestingly, dyslipidemia in CsA withdrawal patients does not improve. On the contrary, exposure to higher SRL levels worsens this condition. Figure 2 on the right below, graphically represents the mean SRL levels in groups A (lower line) and B (upper line).

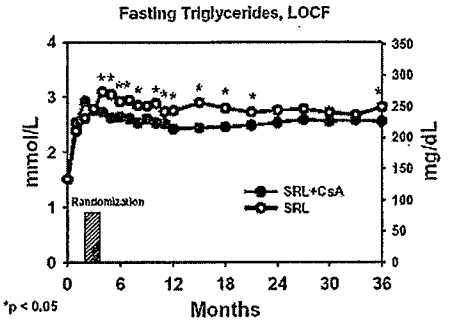
Fig. 11.2.9-a. S-310 FASTING CHOLESTERION ON THERAPY ANALYSIS (Left) AND MEAN ± SE WHOLE BLOOD SIROLIMUS CONCENTRATIONS RENALALLOGRAFT PATIENTS (Right).
From the 3-year safety update S-310, fig 7.3.1A, page 60 and From the Applicant Submission CSR-45863-- Study 0468H1-310-GL, 24 Months, SF 11-4, page 690.

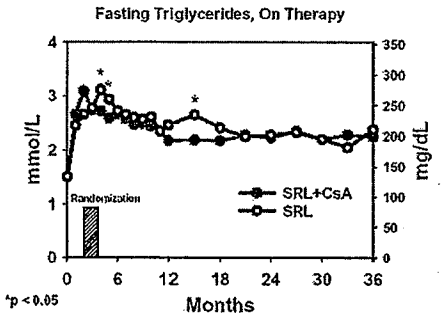




[17] Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285(19) 2486-2497, 2001

Fig. 11.2.9-b. STYDY 310 OBSERVED MEAN VALUES FOR FASTING TRIGLYCERIDES (mg/dL). On Therapy and LOCF. From the 3-year safety update S-310, fig 7.3.2A, pages 63-4





Cholesterol:

In **S-310,** the mean cholesterol values for group B were in the high range[18] (≥6.2 mmol/L) through out the 36-month follow up period. This observation was consistent for the On therapy, LOCF and Completers analyses.

Fasting cholesterol levels were high (> 6.19 mmol/L, 240mg/dL[19]) in both arms post randomization. In 50% to 70% of the on therapy patients were within high range during the first six months, and in 37% to 45% afterwards.

On therapy, LOCF and Completers analysis showed higher mean fasting cholesterol in the CsA elimination group B. This difference was statistically significant at nine months in all analyses when the highest mean sirolimus levels were observed (Fig. 2).

Study 212 showed the same cholesterol elevation pattern as in study 210. Adjusted mean cholesterol levels were significantly higher in group B at month 12 (6.18 mmol/L vs. 6.75 mmol/L groups A and B, respectively). Furthermore 41% and 50 % in groups A and B respectively, were with in the high range (≥ 240 mg /dL, > 6.19 mmol/L)

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[18] Third Report of the NCEP – ATP III. JAMA, 285(19):64-74

[19] To convert Cholesterol to mmol/L divide values by 38.7
ATPIII Classification for Total Cholesterol
Desirable: <200mg/dL (<5.1 mmol/L)
Borderline High: 200-239 mg/dL (5.1-6.1 mmol/L)
High: ≥ 240mg/dL(≥6.1 mmol/L)

Reviewer's Comment: ***The rapid increase in the cholesterol levels in the pre-randomization phase supports a drug related (Rapamune + CsA) effect. The cholesterol levels were persistently above the recommended levels despite any therapeutic intervention (Including statins and other drugs) taken during the study. These levels were significantly higher in the CsA elimination arm, group B at different time points and were associated with an increased exposure to sirolimus.***
The long-term effect of higher serum lipid concentration on cardiovascular risk and chronic allograft nephropathy (CAN) in this transplant population is not well established. There is no apparent deleterious effect on patient and graft survival at 36 months in this group. Further information at 5 years will better define the potential impact of this observations.

High-density Lipoprotein (HDL) Cholesterol:
S-212 and S-310 showed higher HDL-cholesterol levels in group B. Mean values in **S-310** mean values for fasting HDL cholesterol were above 50 mg/dL in both groups from 2 to 24 months (recommended: > 40 mg/dL).
S-212 At month 12, 23.3% and 30.5% of group A and B patients, respectively, had high HDL-cholesterol levels above 1.6 mmol/L. (> 60 mg/dL).

Low-density Lipoprotein (LDL) Cholesterol:
Mean values were above the 100 mg/dL (Optimal: < 100mg/dL, Borderline high: 130-159 [20]) in both groups and not significantly different from 6 through 24 months. Most patients were in the above optimal or borderline high range. During the second year 21% to 28 % of patients were in the high range (>4.1 mmol/L, >159 mg/dL). These rates were similar between the two groups and non- statistically significant.

Triglycerides[21]:
On therapy patients with in the high range, as defined by the sponsor (4.51 to 11.29 mmol/L)(399.5 to 1000mg/dl) represented ≤ 13% at any time point. This group with high triglycerides levels, presented higher rates in group B at any time point post-randomization, these rates were statistically significant at 12 and 18 months.
On-therapy, completers and LOCF data indicate that triglycerides mean values were higher in group B with mean values ≥200 mg/dL (High triglycerides value) at any time point following randomization.
LOCF analysis showed mean values > 200 mg/ dl (High triglycerides levels) in both groups and statistically significant higher values in group B from month 4 through month 24.

Reviewer's Comment: ***NECP-ATP III defines high triglycerides cut-point values between 200-499 mg/dL (2.25 – 5.63 mmol/L). Therefore the cut point used by the***

[20] Third Report of the NCEP. JAMA, 285(19):64-74
[21] The NCEP-ATPIII classification for triglycerides is as follows:
Normal < 150 mg/dl (< 1.7 mmol/L)
Borderline-high 150 - 199 mg/dL (1.7 - 2.2 mmol/L)
High: 200 - 499 mg/dL (2.3 - 5.63 mmol/L)
Very high ≥ 500 mg/dL (≥5.64)

sponsor to characterize a normal-borderline range (≤ 4.5 mmol/L, 398.7 mg/dL) do not correspond to this classification.

Table11.2.9-1. NUMBER (%) OF PATIENTS WHO RECEIVED LIPID-LOWERING AGENTS, BY TREATMENT GROUP (24 MONTHS) From Protocol 0468H1-310-GL, Table 8.3B, page 104 and 0468E1-212-GL, tables 8.3A and 8.3B, pages 73 and 74.

	Study 310 (24 months)			Study 212 (12 months)		
	Nonrandomized SRL + CsA (n = 95)	Group A SRL + CsA (n = 215)	Group B SRL (n = 215)	Nonrandomized (n = 49)	Group A SRL + CsA (n = 97)	Group B SRL (n = 99)
Before study						
Any lipid-lowering agent	28/95(29)	41/215 (19)	40/215 (19)			
HMG CoA reductase	25/95 (26)	32/215 (15)	36/215(17)			
On study						
Any lipid-lowering agent	37/95 (39)	181/215 (84)	185/215 (86)	27/49 (55)	59/97 (61)	69/99 (70)
HMG CoA reductase	32/95 (34)	159/215 (74)	161/215 (75)		55/97 (57)	64/99 (65)

a) only cholesterol an Cholesterol and triglyceride reducers

Before enrolment , a lipid-lowering agent was used by 19% of the patients. During the study, the use lipid-lowering agents was 84% in group A and 86% in group B.
There were 2 cases of rhabdomyolysis reported.

Reviewer's Comment: ***The Copenhagen Male Study (8-year follow-up of 2906 white males) found that the relative risk for coronary events in patients with high triglycerides levels (Average = 2.45 mmol/L,) was more than twice than that for the lowest triglycerides levels (0.88 mmol/L)[22]. In S-310 cholesterol and triglycerides level remain with in the high or very high range despite therapeutic interventions. On the other hand hypertriglyceridemia has been associated with insulin resistance, hyperinsulinemia, poorly controlled diabetes, central obesity but specially increased cardiovascular risk, even when correcting for high-density lipoprotein cholesterol[23]. While TG values ≥200 mg/dL (≥ 2.3 mmol/L) are considered high in the NCEP-Adult Treatment Panel guidelines (ATP), it remains controversial at what level TG are associated with cardiovascular risk.***
Copenhagen study found that values above 1.6 mmol/L (142 mg/dL) resulted in a greater than twofold risk for incipient CAD.

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[22] Jeppesen J et al: Triglyceride concentration and ischemic heart disease. An eight-year follow-up in the Copenhagen Male Study. Circulation 97:1029, 1998

[23] Hokanson JE, Austin MA: Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: A meta analysis of population-based prospective studies. J Cardiovasc Risk 3:213

The renal transplant population face the coexistence of multiple cardiovascular risk factors (Diabetes, hyperinsulinemia / insulin resistance, hypertension, dyslipidemias etc.) that create a complex profile to evaluate. The contribution of the high lipid level in CsA withdrawal population will require further study for a better characterization of its long term consequences.

Liver Enzymes:

In **S-310**, elevations of cytosolic enzymes (LDH, SGOT/AST, and SGPT/ALT) have been observed in sirolimus-treated patients. Patients in group B had significantly higher mean aminotransferase enzymes (SGPT/ALT and SGOT/AST) values from 6 through 36 month. More than 5 times upper limit elevations in SGPT/ALT was present in 6 patients vs. 8, groups A vs. B, respectively.

In **S-212**, adjusted mean values were statistically significantly higher in group B patients than in group A patients for AST at 2, 3, 6, and 9 months, and for ALT at 2, 3, and 6 months.

Reviewer's comment: In S-310 and S-212, sirolimus has been associated with ALT / AST elevations. In most cases this event was transient but it required discontinuation in 7 patient in S-310. (5/7 of the discontinued patients improved after sirolimus was discontinued). Aminotransferases elevations due to hepatotoxicity from sirolimus therapy can be confounded by concomitant liver disease e.g. viral hepatitis and other hepatotoxic medications. Therefore, drug induced hepatitis requires a careful evaluation. For further detail please see:

- **ANALYSIS ON DISCONTINUED PATIENTS : On-Therapy, Completers, and LOCF Analyses for Selected Laboratory Parameters** *sections.*

Blood Pressure:

Reviewer's comment: In S-310, Mean systolic and diastolic blood pressures were either numerically or significantly lower in Group B patients than those in group A at months 6 through 36. This benefit was not observed in patients from S-212 in which mean systolic and diastolic pressures were similar across arms at month 1 through 12.
In S-310 There were significantly fewer reports of new onset hypertension in group B versus group A by 24 months (8.8% versus 21.4%, respectively). Similarly, by 24 months significantly fewer patients in group B were receiving antihypertensive medications (96% versus 88% in groups A and B, respectively).

Body weight:

Weight gain was numerically higher in group A and we agree with the sponsor that this could be explained by a greater percentage of male patients included in group A.

11.2.10. *REVIEWER'S SUMMARY AND CONCLUSION ON SAFETY S-310 and 212:*

Discontinuations:

- *Discontinuations in an open label studies e.g. S-310 and 212, should be evaluated with caution.*
- *Adverse reaction and unsatisfactory response were the most common causes of discontinuation in both studies and across treatment arms.*
- *In S-310 post-randomization phase, 48% of patients from group A and 38% from group B (p = 0.041) discontinued treatment at 36 months follow-up.*
- *Abnormal kidney function and CsA toxicity were the main adverse events (AE) that lead to discontinuation in group A, while abnormal liver function tests and Dyslipidemias were the principal AE for discontinuation in group B. Overdose (CsA toxicity) in group A, was the only cause for discontinuation that reached statistical significance. (Please see* **ANALYSIS ON DISCONTINUED PATIENTS in this review)**

Treatment-Emergent Adverse Event:

- *TEAEs profile was similar to that seen in previous sirolimus phase 3 studies. The most common TEAEs occurring prior to randomization in S-310 were hypercholesterolemia, hypertriglyceridemia, urinary tract infection, hypertension, peripheral edema, diarrhea, increased creatinine, and anemia.*
- *TEAEs incidence in Group B was significantly higher for thrombocytopenia, hypokalemia, increased liver transaminases, ileus, and abnormal healing compared with group A. On the other hand there were significantly fewer cases of CsA toxicity, hypertension, hyperuricemia, creatinine elevation, edema, cataract, abnormal kidney function, and toxic nephropathy in group B compared with group A.*

Infections:

- *Excluding herpes zoster and Fungal dermatitis, there were no significant differences across arms in the rates of infections and severe life threatening infections by The COSTART system*
- *Higher rates in herpes zoster infection in group A, S-310 and fungal dermatitis in group B, S-212 were observed. However, the clinical impact of these differences is not a major concern.*
- *Pneumonia was more frequent in group B while herpes zoster, was more frequent in group A. Most cases of pneumonia resolved with anti-infective therapy. Other types of infections were similar in both groups.*
- *Culture, serology or biopsy was not required to document or include an event as a TEAE related to infection. Therefore, results regarding etiology, should be evaluated with caution.*

Malignancies:

- *The overall malignancy rate was numerically lower in the CsA elimination arm.*
- *TEAE rates related to malignancies at 36 months were 11.2% versus 5.6% group A versus group B, respectively, p = 0.054*

- *Basal cell carcinoma* (BCC). *was the most frequently reported malignancy in group A (4.7% versus 2.3% , group A versus group B, respectively). This type of cancer accounts for 70 to 80% of non-melanoma skin cancers, are non-aggressive and are highly curable. On the other hand Squamous cell carcinomas (SCCs), were more frequent in group B (1.9% versus 2.3% , group A versus group B, respectively. This type of malignancy accounts for 20% of non-melanoma skin cancers. However, they are more significant because of their ability to metastasize and are highly curable when detected and treated early. In summary, SCC in clinically more relevant than BCC.*
- *Four cases of Lymphoma / lymphoproliferative disease were reported, three of them in group A. We cannot draw any definitive conclusions based on this 4 cases.*

Renal function:

- *Renal function was significantly better in the CsA elimination arm (group B), than among those who continued to receive CsA plus SRL (group A). We agree with the applicant that CsA withdrawal, in the populations studied, is associated with superior renal function through 36 months posttransplantation compared with the patients that continue on CsA + SRL combination.*
- *Group B also showed lower serum uric acid, phosphorus, potassium higher serum magnesium than group A*
- *ITT analysis showed that the difference in mean slopes of GFR over time between groups (A-B) was statistically significant from 6 to 36 and 12 to 36 month periods. The main contributing factor for the difference between group slops is the deterioration in renal function over time in the CsA + SRL group (A significantly negative slope change in group A and a numerically positive the mean slopes change in group B)*
- *We agree with the sponsor that the baseline quartile analysis supports that all group B randomized patients might benefit from CsA elimination, irrespective of their baseline renal function.*

Fasting Serum Lipids:

- *Dyslipoproteinemia was routinely treated in the study population; therefore, the studies results reflect the effect of the therapeutic intervention.*
- *There was rapid increase in the cholesterol and triglycerides levels in the pre-randomization phase S-310, suggesting a drug related (Rapamune + CsA) effect.*
- *The cholesterol and triglycerides levels were persistently above the recommended levels despite therapeutic intervention occurring during the study (Including statins and other drugs). These levels were higher or significantly higher in the CsA elimination arm, group B, and were associated with an increased sirolimus exposure.*
- *CsA withdrawal with a concomitant increase in SRL dose, does not provide any improvement for the patient's dyslipoproteinemia. On the contrary, it may*

require an increase in dose of the lipid-lowering agent or other therapeutic interventions.

- *Mean HDL-cholesterol was higher in group B, and the calculated mean LDL-cholesterol levels were not significantly different between the groups.*

Liver Function Tests and Other Hematological Parameters:

- *Serum aminotransferases and LDH presented significantly higher mean values in group B. Also more group B patients discontinued due to hepatic-related events (1 versus 6 patients, group A versus group B).*

- *The mean hemoglobin concentration was mildly and significantly lower in group B at early time points following randomization. This difference was not clinically significant.*
- *Mean platelet counts were significantly lower in group B following randomization, and this difference decreased over time. This difference was not clinically significant and it did not resulted in any increased risk for bleeding.*

Blood Pressure:

- *In S310, mean systolic and diastolic blood pressures were significantly better in Group B patients from 6 through 36 months follow up. This benefit was not observed in patients from S-212 in which mean systolic and diastolic pressures were quite similar across arms and through out the study period.*

[ ]

12. ANALYSIS ON DISCONTINUED PATIENTS STUDIES 310 AND 212

Action item #2 from the February08, 2002 FDA-approvable letter:
"Address the impact of lost patients including disproportionate discontinuation and dropout in the two arms of the studies on the conclusions that may be made regarding the safety of the two regimens"

The initial submission for the Rapamune® maintenance regimen (RMR) analyzed the outcome at 24 months in patients who had first BCAR between randomization and month 12 in S-310. The numbers of deaths and graft losses were similar between groups A and B. However the number of discontinuations among rejectors was higher in group B (18/21) compared with group A (6/11). This difference raises the concern about the significance and impact of these differences on the safety conclusion drawn from this study. Dropouts and discontinuation after randomization could influence the interpretation of results in the on therapy analysis. To explore this possible influence, the applicant submitted the discontinued patient analyses on pivotal **S-310** (24-months analysis and 36-months summary) and the supportive CsA elimination **S-212.**

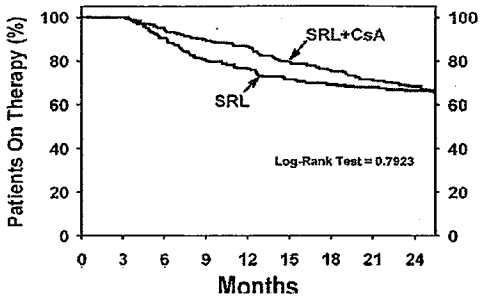
DISCONTINUATIONS: S-310 (36-month) and S-212 (12-month) Data Analysis.
The overall rate of discontinuation in **S-310,** was 51% (269/525) at 36 months and 30% (74/246) at 24 months in **S-212.**
In **S-310,** 18% (95/525) of patients were discontinued before randomization..
Post-randomization, 103/215 patients (48%) from group A and 81/215 (38%) from group B (p = 0.041) discontinued treatment by 36 months.
Adverse reaction and unsatisfactory response were the most common causes of discontinuation in both studies and across arms (See table 12-1).

Table12-1 NUMBER (%) OF PATIENTS WHO DISCONTINUED TREATMENT DURING THE STUDY BY REASON FOR DISCONTINUATION, AND BY TREATMENT GROUP: S-310 AND S-212

Reason for Discontinuation	S-310 (36-months)			S-212 (379 days)		
	Non-rando SRL+CsA	Group A SRL+CsA	Group B SRL	Non-rando SRL+CsA	Group A SRL+CsA	Group B SRL
	95	**215**	**215**	**49**	**97**	**100**
Adverse reaction*	70 (74%)	68 (32%)	54 (25%)	20 (41%)	12 (12%)	12 (12%)
Unsatisfactory response – efficacy*	12 (13)	15 (7)	11 (5)	3 (6)	5 (5)	4 (4)
Patient request and other causes*	7 (7)	16 (7)	11 (5)	5 (10)	3 (3)	10 (10)
Total**	95(100)	103 (48)	81 (38)	28 (57)	20 (21)	26 (26)

Modified from Table 2A, Discontinued Patient Analysis 3-yrs safety update, page 9, S-310 and Table 8.1.1A. , Discontinued Patient Analysis, page 56, S-212)
****Total patients discontinued, (%)**
* **Patients discontinued per reason, (%)**

Fig. 12-a PATIENTS REMAINING ON THERAPY AT 775 DAYS, STUDY 310
(From Discontinued Patient Analysis: Fig. 2.1A, page #) (Applicant's analysis)



Reviewer's Comment: *In S-310, the number of discontinued patients was significantly higher in group B at 12 months. (18 versus 27, group A versus group B, respectively, p = 0.027). Open label studies, may introduce potential for bias in patients evaluation and it could be a partial explanation for the disproportionate rate of discontinuation at 12 months. However, at 24 months, the number of patients on therapy was similar in both groups (141 and 143 in groups A and B, respectively) (Fig.1).*

The number of discontinuations continue to increase in group A and by 36 months follow-up post transplantation, significantly higher discontinuation rate occurred in group A. At the end of this period, 52% (112/215) of patient in group A and 62% (134/215) in group B remained on therapy.
In contrast, in S-212 the total rate of discontinuation was higher in group B.
Adverse reactions were the most common cause of discontinuation in both S-310 and S-212.
In S-310, adverse reactions rates were higher in group A (32%) compared to group B (25%) in S-310 and similar across treatment arms in S-212. Adverse reactions and unsatisfactory response rates were balanced across arms (see Table 1).

12.1. Demographic and Other Baseline Characteristics of Discontinued Patients and Donors: Studies 310 and 212:

Reviewer's comment: *The discontinued patient demographic characteristics in groups A and B were not significantly different (Sex, ethnicity, age, height, weight, primary or secondary Transplant, CMV status, HLA mismatches, and Primary etiology of ESRD) in both studies 310 and 212.*
The characteristics of renal allograft donors of patients who discontinued were similar between the two groups including HLA mismatches, ethnic origin, age, CMV status, and source of donor organ.
In S-310, ischemia time was significantly longer in group A vs B (3.5 hrs difference) and in S-212, there were significantly more donors who where CMV negative in group A. We agree with the applicant that these differences are not clinically relevant.

12.2. Adverse Events Which Led to Premature Patient Withdrawal S-310 and S-212.

Table 12.2-1 NUMBER (%) OF PATIENTS REPORTING ADVERSE EVENTS THAT CAUSED DISCONTINUATION POST-RANDOMIZATION FROM S -310. (36-months follow up)

Adverse Event	Group A SRL + CsA n=215	Group B SRL n=215	A vs. B p-Value
Overdose (CsA toxicity)	**8(4)**	**0**	**0.007**
Abnormal kidney function	11 (5)	3(1)	0.053
Toxic nephropathy	3(1)	0	0.248
Abnormal liver function test	0	3(1)	0.248
Nervous system disorders	5(2)	0	0.061
Pneumonia	5(2)	5(2)	1.000

Reviewer's comment: ***The main adverse events that caused discontinuation post-randomization in S-310 are listed in table 2. Discontinuation rates were higher in group A for CsA toxicity (8 case p= 0.007) and Abnormal kidney function (11 cases p= 0.053, while abnormal liver function tests and Dyslipidemias (hypercholesterolemia (6 cases, p > 0.05) and hypertriglyceridemia (6 cases, p > 0.05)) were the principal adverse events thadt le to discontinuation in group B.***

12.3 Renal Function:

In **S-310**, the data for the ITT analysis was retrospectively collected in discontinued patients. Serum creatinine values were collected in 96.1% (399/415) and 94.2% (374/397) of patients with a functioning graft at months 12 and 24, respectively. In **S-212**, serum creatinine values were available in 90% or more of the ITT population.

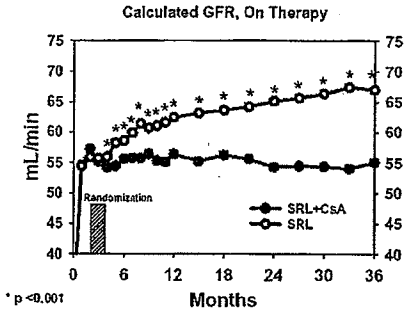
Table 12. 3-1. ITT ANALYSIS FOR CALCULATED NANKIVELL GFR (mL/min) S-310 AND 212 (Modified from sponsor's submission **Discontinued Patient Analysis** table 3.5.1.2A, page 64 and table 7.1.2B 3-Year Safety Update Study 0468H1-310-GL, page 43)

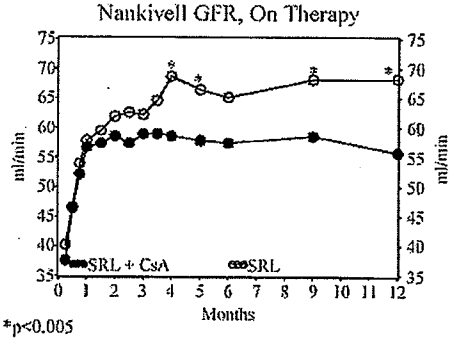
	Study 310**		Study 212***	
Time Posttransplant	**Group A SRL+ CsA**	**Group B SRL**	**Group A SRL+ CsA**	**Group B SRL**
Month 6	**55.35** ±1.35 (189)*	**58.10** ±1.31 (191)	**55.87** ± 1.89 (93)	**64.23** ± 1.79 (95)
Month 12	**53.17** ±1.46 (208)	**59.25** ±1.46 (203)	**56.36** ± 1.98 (91)	**65.27** ± 2.01 (91)
Month 24	**48.38** ±1.67 (203)	**58.35**±1.60 (201)		
Month 36	**47.26±1.83 (194)**	**59.38±1.82 (194)**		

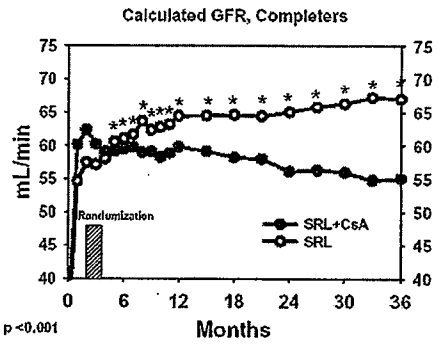
* Mean ± SEM (Number of observations used for the mean)
** A vs B, ANCOVA p-value<0.001 at 6,12, 24 and 36 months
*** A vs B, t-test p-value = 0.009 at 6 and 12 months

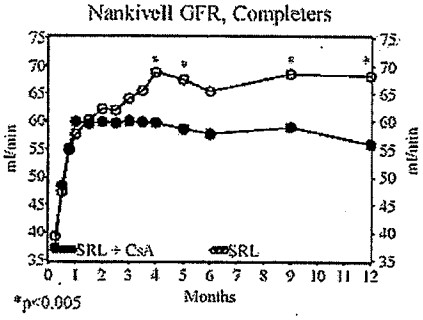
NDA 21-083/S-006
NDA 21-110/S-004

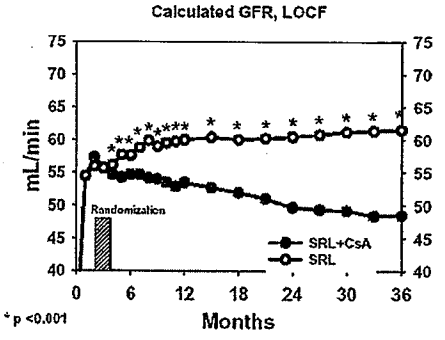
Figure 12. 3-a. INCLUDES THE GRAPHIC REPRESENTATION OF MEAN GFR OVERTIME (On-Therapy, Completers and LOCF analysis). **S-310 AND S-212**
From sponsor's submission Discontinued Patient Analysis figures 3.5.1.2A, pages 65 and 66, and 3 years data safety update figures 7.1.2A, Pages 43 and 44.

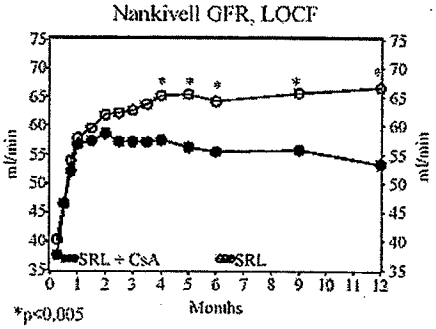












Reviewer's comment: ***ITT, on-therapy, completers, and LOCF analysis for GFR showed that GFR was significantly better in group B compared to group A in both S-310 and S-212. All analyses showed the similar trends over time, suggesting that discontinuation had no impact on the overall conclusions drawn from GFR analyses. On-therapy, completers, and LOCF analyses on GFR for both S-310 and 212 illustrate an increasing difference in renal function over time between group A and B. This difference is dependent on GFR improvement in the CsA elimination arm, and GFR decline over time in group A (SRL+CsA).***

Similarly to the on-therapy, completers, and LOCF analyses, the ITT analysis also illustrate a significant increasing difference in GFR between treatment arms over time. However, in the ITT analysis the difference between arms is mainly dependent on GFR decline overtime in group A (SRL+CsA).

In summary, the ITT analysis clearly demonstrates that GFR decline in group A is the main contributing factor for the difference in GFR between groups and discontinuations did not compromise the overall conclusions drawn from the GFR analysis.

12.4. On-Therapy, Completers, and LOCF Analyses for Selected Laboratory Parameters

Phosphorous, Potassium, Magnesium and Uric Acid: From randomization through month 24, group B had significantly lower mean values for phosphorus, potassium and uric acid and significantly higher values for magnesium than group A.

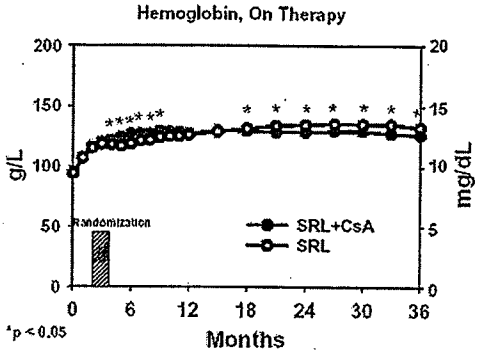
Hematology:

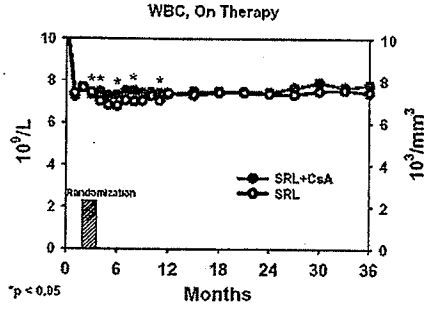
Hemoglobin: In both S-310 and S-212 and across arms, hemoglobin mean values increased after transplantation and reach values ≥ 120g/L at 6 months approximately. After randomization were significantly lower mean hemoglobin values in group B during the first 12 months compared to group A. This observation reversed and by the end of the 24 months, slightly higher mean values were observed in group B.
In **S-212**, hemoglobin mean values were not statistically significantly different between treatment arms any time point.

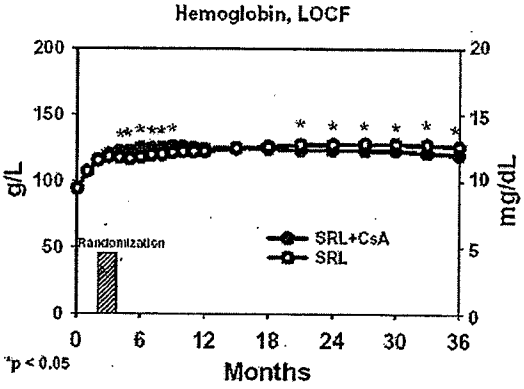
White blood cell counts: In both **S-310** and **S-212,** mean WBC values remain stable and within acceptable range across treatment arms. Mean values were above 6,000 per mm3 in across arms during the follow-up period. One (1) patient in group A discontinued after randomization for leukopenia.

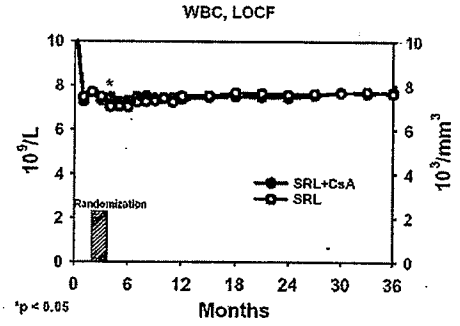
Platelets: Mean values for platelet counts were between 200,000 to 230,000 / mm3 in both studies **S-310** and **S-212** and across arms during the follow-up period. The mean values for both groups were within the normal range, and the differences between them were not clinically relevant.
There were no discontinuations for thrombocytopenia in either group at 24 or 36 months.

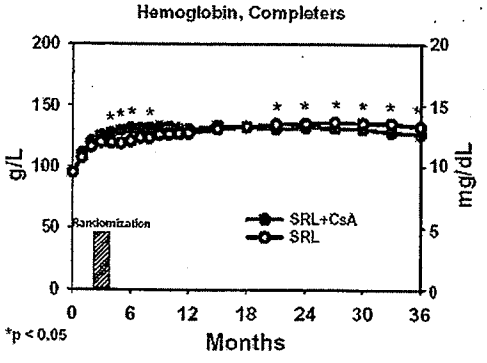
Figure 12.5-a. MEAN HEMOGLOBIN AND WBC OVERTIME.(S-310 On-Therapy, Completers and LOCF analysis). From sponsor's submission 3 years data safety update.

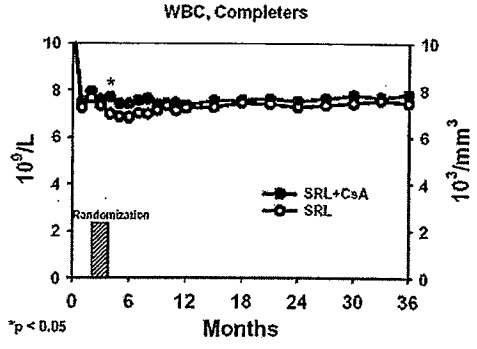












Reviewer's comment: In *S-310*, On-*therapy, completers, and LOCF analyses for each hematologic parameter (hemoglobin, WBC and platelets) showed similar trends over time. The graphic representation of the analyses, presented similar curve shapes across treatment arms suggesting that discontinuations had no impact on the overall conclusions drawn from the on-therapy analyses. In pivotal S-310, hematologic adverse events led to patient discontinuation in 5% and 3%, groups A and B, respectively. One patient in group A and 2 in group B discontinued therapy due to anemia and one patient in group A discontinued for leukopenia.*

Fasting Lipids:

Total cholesterol: Serum cholesterol peaked at month 2, then decreased through month 9, and stabilized thereafter. In **S-310** cholesterol mean levels were modestly higher in group B. The mean values in both arms were between 225 and 239 mg/dL (Borderline High: 200-239). On-Therapy, Completers, and LOCF Analyses showed higher mean cholesterol values in group B. Although this difference was small, it was statistically significant in the completers' analysis up to 18 month.
Triglycerides: On therapy and completers analysis showed that higher mean values in group B after randomization this difference disappeared in the last four months of the study 310. LOCF analysis showed statistically significantly higher mean values in group B trough out the study. Four (4) patients in group A and 7 in group B discontinued because of hypertriglyceridemia between months 3 and 36 months.

Reviewer's comment: On therapy, LOCF and completers analyses for serum lipids showed higher lipid level including HDL cholesterol in the CsA withdrawal arm. The graphic representation of these analyses presented similar curves among them and across arms. Therefore, the conclusions drawn from the on therapy analysis are acceptable despite the patient discontinuations.

LDH and Serum aminotransferases:
In most cases , the increase in ALT or AST were temporary. One patient in group A and 6 in group B were discontinued because of liver aminotranferases elevations. All discontinued patients but 2 presented a significant improvement in aminotransferases level after discontinuation. (See table 4). There were no discontinuations due to elevated LDH.

Table 12.5-b. PATIENTS WHO DISCONTINUED DUE TO ELEVATED AMINOTRANSFERASES

Reason for Discontinuation	Group A SRL + CsA	Group B SRL	AST/ALT Range
Hepatitis B	**1**		**159/158**
Elevated Aminotransferase		1	146/267
Chronic hepatic cytolysis		1	73/182
Elevated liver enzymes		3	21-66/28-141
Drug Induced Hepatitis		1	197/680

Reviewer's comment: On-Therapy, Completers, and LOCF Analyses showed higher mean values in group B vs. A for LDH, SGOT/ AST and SGPT/ALT. AST and ALT values were significantly higher through out the study post randomization in all type of analysis. LOCF and completers analyses corroborate the conclusions drawn from on therapy analysis.

Last Value on Therapy for Laboratory Parameters in Discontinued Patients S-310, 24-Month Analysis:
Last values for discontinued patients analysis, showed significantly higher mean values of Urea, Uric Acid and Phosphorus with a concomitant and significantly higher Calculated Nankivell GFR in group A. SGPT/ALT SGOT/AST were significantly higher in group B.
Reviewer's comment: ***Last values for discontinued patients analysis are in agreement with On-Therapy, Completers, and LOCF analysis and with the overall safety conclusions.***

12.6. ITT Analysis of Severe and Life-Threatening Adverse Events S-310

Severe and life-threatening infection rate was the same in both groups (14.9%). The overall incidences of severe and life-threatening treatment-emergent events excluding infections was similar across treatment arms (36.6% vs.34.9% group A vs group B, respectively ($p = 0.683$). Abnormal kidney function incidence was significantly higher group A (5.1% vs. 0.9%, $p = 0.021$ groups A and B, respectively). There were no other significant differences in the incidence of severe and life-threatening treatment-emergent events between treatment arms.

12.7. REVIEWER'S SUMMARY AND CONCLUSION:

- Discontinuation rates: ***S-310 36-months data analysis showed that discontinuation rates were significantly higher in group A (48% vs. 38 % groups A vs B, respectively, P=0.041). In contrast, S-212 discontinuation rate was higher in group B, but not significantly different from group A. 26% vs 21%, respectively. The observed differences between treatment groups are not clinically relevant.***

- Demographic Characteristics: ***There were no significant differences in the demographic characteristics, primary or secondary transplant, CMV status and primary etiology of ESRD of the discontinued patients in both studies 310 and 212.***

- Adverse Event Leading to Premature Withdrawal (AELPW): ***In S-310, CsA toxicity as an AELPW, was significantly higher in group A (4%) vs. group B (0%), p = 0.007. Study 212 showed no significant differences in AELPW.***

- Renal Function S-310 and S-212: ***Statistically significant better renal function was observed in the On-therapy, completers, LOCF and ITT analyses in the SRL maintenance regimen (Group B) compared with the SRL + CsA combination (Group A). The ITT analysis clearly demonstrates that GFR decline in group A is the main contributing factor for the difference in GFR between groups. We conclude that discontinuations did not compromise the overall conclusions drawn from the GFR analysis regarding the significant difference in GFR between treatment arms.***

- Laboratory Assessments (Excluding serum creatinine): ***On-therapy analyses were complemented with Completers, and LOCF analysis since laboratory data was***

available only for 30 days following patient discontinuation. We agree with the applicant that the results did not show any trend in discontinuations that might suggest a bias affecting the conclusion. There were no clinically meaningful differences between the different type of statistical analyses that would change the conclusions regarding the effects of treatments on laboratory parameters. The differences between groups A and B are expected as a result of treatment effects.(e.g. CsA related toxicity events in group A)

Study 310 ITT Analysis of Severe and Life-Threatening Treatment-emergent events:

- *CsA toxicity incidence was significantly higher in group A. There were no other significant differences in the incidence of severe and life-threatening treatment-emergent events between treatment arms. This observation is expected given the nephrotoxic effect of CsA.*

In conclusion, ITT, completers, LOCF, and last values on therapy analyses complemented the on-therapy analyses. Similar conclusions are drawn from all types of analyses and we agree with the applicant that lost or discontinued patients have not introduced bias that impacted on the safety conclusions drawn from on therapy analyses.

13. IMPACT OF REJECTION ON RENAL FUNCTION ITT ANALYSES FROM STUDIES 212, 310, 301AND 302

It is well known that AR has adverse consequences on renal function and long-term graft survival, and it is expected those deleterious effects to be directly related to the extent of damage caused during these AR events.
Results from S-310 and 212 showed increased incidence of BCAR episodes following CsA withdrawal in group B compared with CsA + SRL arm, group A. Therefore, at the pre-NDA meeting held on July 29, 2002, the agency asked the applicant to address the effects of AR on renal function in order to asses the degree of damage sustained in the subset of patients who presented BCAR after CsA withdrawal.

Agency requests and action items at the pre-submission meeting on Jul 29, 2002:

"Analyze serum creatinine and glomerular filtration rates (GFR) for Studies 310 and 301 stratified by rejector versus non-rejector."

"Wyeth agreed to submit new analyses of all relevant studies stratified by the patients' rejector status."

Tables 13-a and 13-b summarize the mean Nankivell GFRs of patients who did and who did not experience acute rejection, stratified by randomized groups (Studies 310 and 212)

Table 13-a. OBSERVED MEAN VALUES (± SEM) FOR NANKIVELL GFR (mL/min) IN PATIENTS WHO DID AND DID NOT EXPERIENCE A PRIMARY BCAR: S-310, ITT ANALYSIS (24 MONTHS) AND S-212 (12 MONTHS)

Study Rejection Period	BCAR	Group A SRL + CsA	Group B SRL	p-Value[b] Group A Nonrejectors vs Rejectors	p-Value[b] Group B Nonrejectors vs Rejectors	p-Value[b] Group A vs Group B
310 Rejection Post-randomization	**No**	49.6 ± 1.7 (192)	60.8 ± 1.6 (180)	0.008**	<0.001***	<0.001***
	Yes	27.5 ± 7.1 (10)	35.9 ± 5.3 (19)			**0.256**
310 Rejection Post-transplantation a	**No**	51.4 ± 1.7 (172) c	61.3 ± 1.7 (159)	0.025*	0.026*	<0.001***
	Yes	33.2 ± 4.3 (30) c	46.7 ± 4.0 (40)			0.005**
212* Rejection Post-transplantation a	**No**	57.4 ± 2.3 (75)d	70.9 ± 1.9 (70)	0.027*	<0.001***	<0.001***
	Yes	44.9 ± 5.7 (16)	45.4 ± 4.3 (21)			**0.943**

Modified from TABLES 2.1.2A and 2.12B, IMPACT OF REJECTION ON RENAL FUNCTION, Pages 11 and 14.

a: Any primary rejection from the time of transplantation.
b: p-value; *p <0.05, **p < 0.01, *** p < 0.001.
c: Number of observations used to calculate mean.
* Randomization 2-7 days posttransplant

Table 13-b. OBSERVED MEAN VALUES (± SEM) FOR NANKIVELL GFR (mL/min) IN PATIENTS WHO DID AND DID NOT EXPERIENCEA PRIMARY BCAR: STUDY 301AND 302, ITT ANALYSIS

Study (Rejection Post-transplantation) a	BCAR	SRL (2mg/day) +CsA	SRL (5mg/day) +CsA	AZA (301) +CsA or Placebo(302) +CsA	p-Value[d] Nonrejectors vs Rejectors	p-Value[d] SRL 5 mg/day vs AZA
301(24 MONTHS)[a] **SRL 2: n=284 SRL 5: n= 274 AZA: n=161**	**No**	58.7 ± 1.7 (176) c	53.8 ± 1.6 (187)	63.0 ± 2.5 (96)	SRL 2:= 0.746 SRL 5:= 0.056 Aza: = 0.461	0.002*
	Yes	57.5 ± 3.3 (44)	46.0 ± 3.3 (35)	60.6 ± 2.1 (36)		0.001*
302(36 MONTHS) b **SRL 2: n=227 SRL 5: n= 219 Placebo: n=230**	**No**	56.7 ± 1.7 (113) c	56.3 ± 1.9 (112)	61.4 ± 2.5 (54)	SRL 2: <0.001* SRL 5: <0.001* Placebo: =0.002*	0.122
	Yes	34.1 ± 3.3 (70)	28.6 ± 3.6 (65)	44.4 ± 4.8 (48)		0.008*

Modified from TABLES 2.2.2A and 2.22B, IMPACT OF REJECTION ON RENAL FUNCTION, Pages 20 and 22.

a: Five patients, with missing acute rejection status, were excluded from the analysis.
b: Three patients, with missing acute rejection status, were excluded from the analysis.
c: Number of observations used to calculate mean.
d: t-test p-value

13.1. REVIEWER'S SUMMARY AND CONCLUSIONS:

Acute rejection was associated decreased renal function in all randomized cohorts in studies 310, 212, 301,and 302 (Including the comparator groups azathioprine and placebo). The impact was more pronounced among patients randomly assigned to receive the combination of CsA + SRL, particularly at a higher dose. Similarly, freedom from rejection was associated with better renal function in these studies.

- ***In both S-310 and 212, patients experienced BCAR post-transplantation showed a significantly lower mean GFR in both randomized cohorts compared to those who were rejection free. As expected, acute rejection has a deleterious effect on GFR that is amplified if the patients continue in the CsA + SRL combination.***
- ***After randomization[24], patients in S-310 group B that experience primary BCAR showed a numerical but not significant benefit in mean GFR compared to the patients who continued on CsA + SRL (Group A). Similarly, in S-212 patients who experience primary BCAR, showed similar mean GFR across arms***
- ***Similarly, in S-212 patients who were randomized to the CsA withdrawal arm and rejected, showed similar mean GFR as patients randomized to group A and experience primary BCAR. (Group B/rejectors, 45.4 ± 4 mL/min versus group A/rejectors 44.9 ± 5.7 mL/min, P=0.943).***
- ***Even though, there was a significant GFR benefit among the rejectors randomized to the CsA withdrawal arm in S-310, the data from S-212 do not support this observation. Therefore we can conclude that CsA withdrawal benefit on GFR among rejectors was not clearly demonstrated. The results suggest that the impact of AR on renal function overrides the salutary effects of CsA withdrawal as a result of kidney damage during the rejection event.***
- ***Continuing treatment with CsA + SRL combination adversely affect renal function at 2 years posttransplantation. The induced decline in GFR by CsA is additive to the impact of acute rejection.***
- ***Studies 301 and 302 showed that renal function was numerically and/or significantly lower among patients who experienced BCAR who were randomly assigned to SRL + CsA combination (at 2 and 5 mg doses) compared with that of the corresponding rejector subsets assigned to AZA (S-301) or placebo (S-302).***
  We cannot exclude the possibility that the type of late rejection that emerges under CsA + SRL may be more damaging than the kind that emerges early under CsA + Aza or CsA + Placebo.
  Patients who had experienced acute rejection, the mean Nankivell GFR was numerically higher in the placebo cohort than in the sirolimus 2-mg/day cohort, and significantly higher in the placebo cohort than in the sirolimus 5-mg/day cohort. This observation suggests a sirolimus dose related enhanced CsA-nephrotoxicity. This pharmacokinetic interaction between CsA and SRL has been previously described.[25]

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[24] **S-310:** Randomization occurred 12±2 weeks after surgery and CsA withdrawal @ 3-4th months after surgery

[25] Podder H, Stepkowski SM, Napoli K, Kahan BD. Pharmacokinetic interactions between sirolimus and cyclosporine exacerbate renal dysfunction. Transplant Proc. 2001 Feb-Mar;33(1-2):1086.

NDA 21-083/S-006
NDA 21-110/S-004

14. CHARACTERIZATION OF REJECTION PATTERNS IN STUDIES 301-US 302-GL AND 310-GL

In studies 301 and 302, primary BCAR continued to occur through 24 to 36 months post-transplantation, respectively. FDA was interested in having the sponsor consider the timing of CsA withdrawal in light of these late rejections and determine which patients on the combination of sirolimus and CsA experienced late acute rejection.

Agency request at the pre-submission meeting on July 29, 2002:
"Consider the timing of cyclosporine (CsA) withdrawal. It would be useful to determine which patients experienced an acute rejection while on the combination of sirolimus and CsA (this population may have differed between studies 301 and 310). Wyeth agreed to review the data for studies 301 and 302 and separate out those patients who could be considered low- and high-risk as well as stratified by rejector status".

FDA suggested that Wyeth should use the criteria established for study 310 to assist in defining those patients who were at low and high risk for rejection, while considering the timing of the withdrawal of CsA.

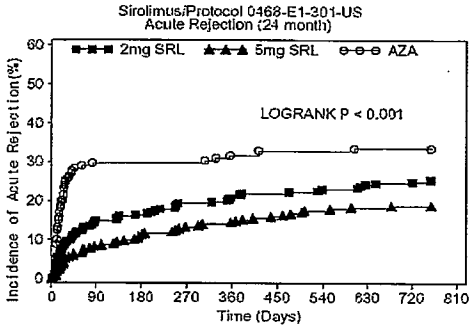
Table 14-1. PRIMARY BCAR RATES FOR STUDIES 301, 302 AND 310.

Study	Time of Randomization	Sex & Race	Groups (n)	BCAR 0 to 6 months	BCAR 0 to24 months	BCAR 6 to 24 months	BCAR 0 to 36 months	BCAR 6-36 months	BCAR 12 to 36 months
301-US (719) c,d.	24-48 hours Post-transplant 2:2:1 SRL 2: SRL 5: AZA	W=406 (56%) B=166 (23%) H=105 A=27 Other=15	SRL -5 a. (n=274)	11.3%	17.5%	**6.2%**			
			SRL -2 a. (n=284)	16.5%	23.6%	**7.1%**			
			AZA a. (n=161)	29.2%	32.3%	**3.1%**			
302-GL (576) d.	Pre-transplant radomization 2:2:1 SRL 2: SRL 5: Placebo	W=450 (78%) B=66 (11%) A=20 H=12 AU=4 Other=24	SRL -5 a. (n=219)	16%			27.4%	**11.4%**	
			SRL -2 a. (n=227)	21.1%			32.2%	**11.1%**	
			Placebo a. (n=130)	36.9%			43.8%	**6.9%**	
310 (430) c,d.	12±2 wks. CsA withdrawal At 3- 4 months.		CsA+SRL b. (n=215)				14.9%		**1.4%**
			SRL b. (n=215)				20.5%		**0.5%**

a. All groups received CsA and corticosteroids in S-301 and S-302. b. The two randomized groups received corticosteroids. c. Includes both on-therapy after randomization and follow-up after discontinuation periods
d. BCAR Rates excludes lost to follow up
Data on S-301 and 302 is from **Overall long-term patient and graft survival, acute rejection, and serious adverse events summary**, tables 2.1.4.1A and 2.13.1A, pages 17 and 22. Data on S-310 is from Rapamune 3- Year Safety Update Renal Transplant Recipients in Study 0468H1-301-GL, Table 5.2A page 16.

Reviewer's Comment: ***The total primary BCAR rates were higher in the Aza, Placebo and CsA withdrawal arm at 24, 36 and 36 months in S-301, 302 and 310, respectively (See table 1). These treatment arms presented lower rates of late BCAR compared with the CsA + SRL arms in the referred studies. Therefore, when specific periods of time are analyzed, (6-24months in S-301, 6 -36 in S-302 and 12-36 in S-310) the results indicate lower rates of "late" rejection in the Aza, placebo and SRL arms, studies 301, 301 and 310, respectively and do not reflect the entire spectrum of rejection events.***

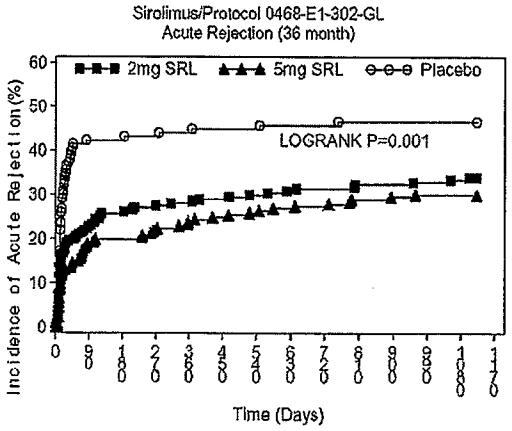
Figure 14-a. From Characterization of rejection patterns in Rapamune® studies 301-us and 302-gl: figures 3.1.2A page 9.



Reviewer's comment: ***The majority of the BCAR occurred within the first 120 days posttransplantation.***
In the sirolimus cohorts, primary BCAR occurred throughout the duration of the 24-months period; while in the Aza arm most of the BCAR occurred in the early posttransplant period and only 5 BCAR occurred after 90 days.

In S-301, SRL 5-mg group had significantly less acute rejections than patients did in the Aza group. The SRL-2-group had numerically less BCAR's than patients did in the Aza group. Except for the proportions of male and female patients (M=469, F=25) in the study, patient demographics were similar among the 3 treatment groups in S-301. 56% of the patients were white, 32% were black, and 65% of the allograft donors were cadaveric.

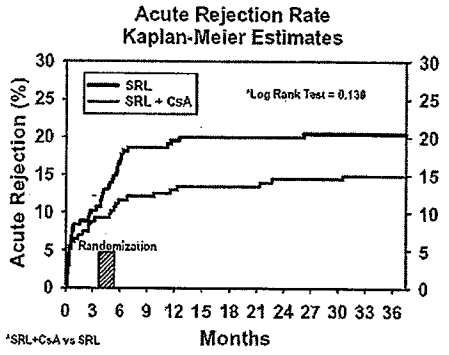
Figure 14-b. From Characterization of rejection patterns in Rapamune® studies 301-us and 302-gl: figures 3.2.2A page 11.



Reviewer's comment: ***In S-302, the differences in BCAR were significantly different among the three groups. SRL-5-mg group had the lowest rate of BCAR.***
The majority of BCAR's occurred within the first 120 days posttransplantation. Only 5 BCAR occurred after 120 days post transplantation in the placebo arm.

In S-302, there were no significant differences in patient or donor demographic characteristics among the 3 groups. 78% of the patients were white, 11% were black, and 77% of the allografts were from cadaver donors.

Figure 14-c. From Rapamune 3- Year Safety Update Renal Transplant Recipients in Study 0468H1-310-GL. Fig 5.2A, page 18.



Reviewer's comment: ***Post-randomization, primary BCAR rates at 36 months were numerically higher in the CsA withdrawal arm, (group B). Most of the primary BCAR occurred during the following three months after CsA withdrawal.***

In S-310, 94% of the patients enrolled were white, and 90% received a primary graft. There were no significant differences between the 2 randomized groups in renal allograft donor demographic characteristics.

Reviewer's Comment: ***In studies 301 and 302 the majority of the primary BCAR episodes occurred within the first 3 or 4 months after transplantation. However, BCAR continued to occur through 24 to 36 months posttransplantation, respectively. Patients on azathioprine in study 301 or placebo in study 302 experienced fewer episodes of late rejection (After 3 or 4 months posttransplantation). Patients in CsA + SRL arm in S-301, S-302, and S-310 presented a similar pattern of late primary BCAR.***
We agree with the sponsor that there was a disproportionately high number of late BCAR studies 301 and 302, in the SRL + CsA groups compared with Aza or placebo groups, respectively.

14.1 Analyses of High Risk Sub-populations:

14.1.1 Analysis by Race S-301 and S-302:

In **S-302** 11% of the patients enrolled were blacks. (The national standard is 22.5% of the kidney transplant recipients[26]).
In **S-301**, 23 % (166) of the patients enrolled were African American. Sixty-three (63) patients were assigned to the SRL-5 group, 62 to the SRL-2 and 41 to the Aza group. The overall primary BCAR rate among black at 24 months was 32.5%.
Acute rejection rate in black patients was either numerically or significantly (Only in S-301 at SRL-2mg dose) higher than that in non-black patients in both **S-301** and **S-302**.
Late acute rejection occurred in black as well as non-black patient populations in both sirolimus treatment groups (2-mg and 5-mg) in each of these 2 studies.

[26] OPTN data as of July6, 2001

14.1.2. Analysis by HLA mismatch S-301 and S-302:

Primary BCAR in patients with ≥ 4 HLA mismatches were either numerically (sirolimus 2-mg dose group in study 302) or significantly (all other treatment groups) higher than the rates in patients with ≤3 HLA mismatches at each sirolimus dose level in both studies. Late primary BCAR occurred in patient regardless of the degree of HLA mismatch

Reviewer's Comment:

In these trials, the only high-risk populations included were black patients and patients with > 3HLA mismatches. Black patients were underrepresented in S- 302 (11%) and S-310 (2% of patients enrolled). There were very few patients with high panel reactive antibodies and patients with re-transplants or multiorgan transplants were not enrolled in these studies.

14.1.3. High Risk Population in Study 310:

94% of all patients enrolled were white, and most (90%) received a primary graft and there were no significant differences between the 2 randomized groups in renal allograft donor demographic characteristics.

Reviewer's Comment: Randomized patients in study 310 were a low-risk selected group in which high-risk patients were auto excluded during the first 90 days pre-randomization phase.

14.2. REVIEWER'S SUMMARY AND CONCLUSIONS ON LATE PRIMARY BCAR[27]

- ***It is difficult to compare the rejection patterns among studies 301, 302, and 310 because of differences in study design (time of randomization, type of patients enrolled etc.).***
- ***A major contributor factor was not clearly identified (e.g. Race, degree of HLA mismatch, demographic characteristics, and on-therapy status) to explain the pattern of late BCAR observed in these studies. However, in studies 301, 302 and 310, the CsA + SRL combination presented a similar pattern of "late primary BCAR's", which are in greater number than in the Aza, placebo or CsA withdrawal arms.***
- ***We agree with the applicant that regardless of the enrollment imbalances among treatment arms in S-301, S-302 and S-310, there was a disproportionate high number of late BCAR in the CsA + SRL groups. Therefore late partial analyses of BCAR e.g.12 to 36 months in S-310, will be including more number of late BCAR in the CsA + SRL combination and less in the CsA withdrawal arm. Similarly, the same type of analyses will exclude the burst of BCAR episodes that occur after CsA withdrawal in S310 (See table 1).***
- ***In summary, partial analyses e.g. 12 to 36 months in S-310 may give a false perspective of the primary BCAR rates, favoring the CsA withdrawal arm with less rejection episodes when in reality the overall rate is higher in this arm. Further investigation is required to better characterize the late acute rejection patterns the CsA withdrawal regimens.***

[27] Late primary BCAR was defined as follows: S-301, BCAR after 90 posttransplantation. S-302, BCAR after 120 days posttransplantation. S-310, BCAR 12±2 week posttransplantation.

15. ITT ANALYSES ON RENAL FUNCTION

- **IMPACT OF CYCLOSPORINE WITHDRAWAL ON RENAL FUNCTION STUDIES 310 AND 212**

- **LONG-TERM RENAL FUNCTION IN PATIENTS RECEIVING CYCLOSPORINE PLUS SIROLIMUS STUDIES 301, 302 AND 309**

Applicant's response to action items 1 and 3 from the approvable letter, February 08, 2002.
"Conduct an intent-to-treat analysis of... the change in renal function over time up to 24 months post-transplantation in Study 310, which would demonstrate sustained improvement in renal function after withdrawal of cyclosporine. This analysis should include measurement of renal function at 6, 12, 18 and 24 months post-transplantation, in all subjects randomized, whether or not they continued on study drug. It is recommended that such analyses include a slope intercept analysis of serum creatinine clearance over time."

"Complete your postmarketing commitment to provide long-term information from studies 301 and 302, including intent-to-treat information on renal function, whether or not patients continued on study drug. The 24-month reports submitted for these studies have only included on-therapy analyses of renal function and therefore do not meet this postmarketing commitment. Include a slope intercept analysis of serum creatinine clearance as well."

Relevant Background:

In the absence of Calcineurin Inhibition, the average time to reach the zenith of renal function after transplantation is 6.8 +/- 3.5 year for cadaveric kidney compared to 4.6 +/- 4.0 years among living donor kidneys[28]. Therefore, we should expect some increase in renal function in the CsA withdrawal arm over time post-transplantation. On the other hand, we know from previous phase III studies (S-301, S-302) that creatinine and GFR worsen over time with a SRL + CsA regimen. It has been suggested that this effect is dose related and involves a pharmacokinetic interaction[29]. In these studies the comparators (CsA +Aza and CsA + Placebo) had superior renal function compared to the SRL + CsA combination.

On therapy and ITT analysis on renal function over time were reviewed from 5 different trials. The **"CsA withdrawal studies" 212** and **310** were analyzed through 12 and 36 months posttransplantation, respectively. Also long-term renal function data of patients on **"CsA plus**

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[28] Brazy PC, Pirsch JD, Belzer FO. **Factors affecting renal allograft function in long-term recipients.** Am J Kidney Dis. 1992 Jun;19(6):558-66.

[29] Podder H, Stepkowski SM, Napoli K, Kahan BD. **Pharmacokinetic interactions between sirolimus and cyclosporine exacerbate renal dysfunction.** Transplant Proc. 2001 Feb-Mar;33(1-2):1086.

SRL administration", studies **301, 302**(through 24 and 36 months posttransplantation, respectively), and study **309**[30] were reviewed.

For patients with graft loss, values of GFR were set to zero at the time of graft loss; following graft loss, this data was not included in the ITT analyses. The GFR mean values for both ITT and On-therapy for S-310 and S-212 are presented in tables 8 and 9 at the end of this section. Each table presents both ITT and On-therapy mean GFR values over time for a better comparison.

16. IMPACT OF CYCLOSPORINE WITHDRAWAL ON RENAL FUNCTION STUDIES 310 AND 212

16.1. Calculated Nankivell[31] GFR: Studies 310 and 212

Table 16.1-1. OBSERVED MEAN VALUES (± SEM) FOR CALCULATED NANKIVELLGFR (mL/min) ITT ANALYSES, STUDIES 310 AND 212

	Study 310 c		Study 212 d	
Time Post-transplant	**Group A SRL+CsA n=215**	**Group B SRL n=215**	**Group A SRL+CsA n=97**	**Group B SRL n=100**
Month 6	55.35 ± 1.35 (189) a	58.10 ± 1.31 (191)	55.7 ± 1.9 (93)	64.2 ± 1.8 (95)
Month 12	53.17 ± 1.46 (208)	59.30 ± 1.47 (202)	55.2 ± 2.2 (91)	65.0 ± 2.1 (91)
Month 24	48.25 ± 1.68 (203)	58.38 ± 1.62 (199)		
Month 36	**47.26±1.83 (194)**	**59.38±1.82 (194)**		
Change in GFR *b*	**-8.09 ml/min**	**+1.28 ml/min**	**-0.5 ml/min**	**+0.8 ml/min**

Modified from table 2.1.1H, Overall long-term renal function summary, page 14 and table 7.1.2B, 3-Year Safety Update Study 0468H1-310-GL, page 43.
a. Number of observations used to calculate mean.
b. Change in GFR in S-310 from 6 to 36 months and S-212 from 6 to 12 months
c. A vs B, ANCOVA p-value<0.001 at 6,12, 24 and 36 months
d. A vs B, t-test p-value = 0.009 at 6 and 12 months

Reviewer's comment: ***The ITT analyses, S-310 and 212 show a statistically significant differences in GFR at 6 and 12 months favoring the CsA elimination arm, group B. This difference increases over time due to GFR deterioration in group A and a concomitant GFR improvement in group B.***
Renal function in the CsA withdrawal arm was significantly superior compared with group A from 6 through 36 months in S-310. We must note, from 12 to 36 months GFR remained

[30] S-309 was a designed to test therapeutic equivalence between the oral solution and the tablet formulation. This study enrolled 477 patients randomly assigned (1:1) to receive CsA and corticosteroids with sirolimus (2 mg/day), administered either as the liquid or tablet formulation.
[31] Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR. **Predicting glomerular filtration rate after kidney transplantation.** Transplantation. 59(12):1683-9, 1995.

practically unchanged in group B and the difference between arms was mainly dependent on GFR deterioration in the CsA + SRL arm. (See table 1, calculated GFR, ITT analysis) After the initial improvement in GFR associated with CsA withdrawal, (Removal of the afferent arteriole vasoconstrictive effect from CsA therapy) the renal function in group B remains stable up to 36 months. S-310 showed a negative (-8 ml/min) change in GFR in group A compared with + 1.28 ml/min in group B from 6 to 36 months.

16.2. Quartile Analysis by Pre-randomization Baseline GFR:

In order to better understand the benefits of RMR on this population, the applicant performed exploratory sensitivity quartile analyses on GFR.
The population in S-310 was divided in quartiles according to the base line pre-randomization GFR and the changes over time were analyzed (table 16.2-1).

Table 16.2-1. QUARTILE ITT ANALYSIS FOR NANKIVELL GFR (mL/min).
MEAN (± SEM) CHANGE FROM BASELINE (PRERANDOMIZATION) TO 36 MONTHS. S-310

Pre-randomization GFR to 36 Months	*Group A SRL + CsA*	*Group B SRL*	*ANCOVA p-Value[a]*
1rst Quartile: ≤ 45 mL/min	-9.6 ± 3.0 (44)	4.4 ± 2.3 (47)	< 0.001***
2nd Quartile: > 45 to 56 mL/min	-10.4 ± 3.0 (46)	6.6 ± 2.8 (48)	0.003**
3rd Quartile: > 56 to 67 mL/min	-7.0 ± 2.2 (51)	7.8 ± 3.0 (52)	0.006**
4th Quartile: > 67 mL/min	-13.0 ± 3.4 (53)	-4.1 ± 3.6 (47)	0.683

Modified from table 7.1.4D Rapamune 3-Year Safety Update Renal Transplant Recipients in Study 0468H1-310-GL, page 52.

Reviewer's comment: ***The quartile ranges and the magnitude of change from baseline GFR over time for the IIT population showed a significant difference between groups A vs B except for the fourth quartile (Best GFR baseline quartile). This quartile was still numerically superior than its counterpart in group A (-13 vs -4.1 ml/min, groups A vs B, respectively)***

The difference between groups is dependent on the GFR deterioration over time in all quartiles in group A and an improvement over time in group B. The improvement in group B dependents on the three lower quartiles. Patients on the best baseline GFR quartile apparently reach GFR zenith earlier in time and the decline became evident at 12 (-1.4 ml/min), 24 months (-3.5 ml/min) and 36 months (-4.1ml/min).

16.3. Slope Analyses on GFR Over Time Studies 310 and 212.

The rate of decline (or improvement) in renal function over time was assessed using slope analysis on 1/ creatinine and calculated GFR (see table 16.3-1.).

Table 16.3-1. ITT SLOPE ANALYSES, NANKIVELL GFR (ML/MIN/YEAR), S-212 AND S-310

Period	*Group A SRL + CsA*	*Group B SRL*	*Difference (A-B)*
S-212, 6 to 12months			
Slope (mean±SEM)	-2.9 ± 2.2	2.7 ± 2.2	-5.6 ± 3.1
# patients to calculate the mean.	(91)	(95)	
95% CIs	(-7.3, 1.5)	(-1.7, 7.0)	(-11.8, 0.6)
p-Value	0.196	0.223	0.077
S-310, 6 to 36months			
Slope(mean±SEM)	-3.037 ± 0.453	0.827 ± 0.449	-3.864 ± 0.638
# patients to calculate the mean.	(213)	(212)	
95% CIs	-3.929, -2.146	-0.056, 1.709	-5.118, -2.610
p-Value	< 0.001***	0.066	< 0.001***
S-310, 12 to 36 months			
Slope(mean±SEM)	-2.781 ± 0.501	0.585 ± 0.497	-3.366 ± 0.706
# patients to calculate the mean.	(205)	(207)	
95% CIs	-3.767, -1.795	-0.394, 1.564	-4.755, -1.977
p-Value	< 0.001***	0.240	< 0.001***

Modified from tables 2.1.2D Overall Long-term Renal Function Summary, table 2.1.2D page 19 and table 7.1.3B Rapamune 3-Year Safety Update Renal Transplant Recipients in Study 0468H1-310-GL, page 47. Random coefficients regression model; *p < 0.05, ** p < 0.01, *** p < 0.001.

Reviewer's comment:

In general, studies 310 and 212 showed similar slope patterns (a negative slope in group A and a positive slope in group B).

S-310: ITT analysis showed that the difference in mean slopes between groups (A-B) was statistically significant from 6 to 36 and 12 to 36 month periods. It also showed a significant negative slopes in group A; however, the mean slopes for group B, although numerically positive, did not showed a statistically significant change in none of the periods analyzed. This observation agrees with the fact that even though, the slopes in group B are numerically positive, the main contributing factor for the difference between group slops is a significant deterioration in renal function over time in the CsA + SRL group.

S-212: This study showed a numerically negative slope in group A and a positive slope in group B over time. The slope changes over time were not significantly different. Similarly, the mean slope difference between groups was not statistically significant.

In summary, S-310 and S-212 the slop analyses showed a significant divergent trend favoring group B. This difference between arms is mainly due to GFR deterioration in the CsA + SRL arm with a GFR decline of -8 ml/min at 36 months posttransplantation.
We are in general agreement with the applicant analyses. See FDA biostatistical review for further details.

17. LONG-TERM RENAL FUNCTION IN PATIENTS RECEIVING CYCLOSPORINE PLUS SIROLIMUS STUDIES 301, 302, 309 AND 311.

Table 17-1 summarizes the characteristics and main differences between studies 301 and 302.

Table 17-1

Study	Design	Primary endpoint	Time of Rando-mization	Stratification	Patients rando-mized	Time of evaluation	Groups** SRL and AZA Doses (n)	Sex & Race
301 US	Prospective, Double blind, comparator controlled	*Efficacy failure within the first 6 months after transplantation	**24-48 hours Post-transplant 2:2:1 SRL 2: SRL 5: AZA**	**Investigator and Race**	**719**	**24 mo.**	**SRL 2mg/day (n=284) SRL 5mg/day (n=274) AZA 2-3mg/kg/day (n=161)**	M=469 F=250 W=406 B=166 H=105 A=27 Other=15
302 AU, CA, EU, US	Randomized, Double blind, parallel group		**Pre-transplant radomization 2:2:1 SRL 2: SRL 5: Placebo**	**Investigator and Donor Origin**	**576**	**36 mo.**	**SRL 2mg/day (n=227) SRL 5mg/day (n=219) Placebo (n=130)**	M=388 F=188 W=450 B=66 A=20 H=12 AU=4 Other=24

*Efficacy failure was defined as the first occurrence of: 1) Biopsy-confirmed acute rejection, 2) graft loss (Physical or Functional (> 56days of continuous dialysis)) or 3) Death

** All groups received CsA and Corticosteroids

17.1. Calculated Nankivell GFR: Studies 301 and 302

Table 17.1-1. CALCULATED NANKIVELL GFR (mL/min): MEAN VALUES (± SEM), ITT ANALISES

Time Post transplant	S-301				S-302			
	SRL 2 mg/day	SRL 5 mg/day	AZA	p-Value a SRL2 vs AZA SRL5 vs AZA SRL2 vs SRL5	SRL 2 mg/day	SRL 5 mg/day	Placebo	p-Value a SRL2 vs Placebo SRL5 vs Placebo SRL 2 vs SRL 5
6 Months	**59.8 ± 1.3 (248)** b	**56.8 ± 1.3 (226)**	**65.2 ± 1.8 (127)**	0.015* <0.001*** 0.088	**54.1 ± 1.5 (203)** b	**52.0 ± 1.6 (181)**	**56.2 ± 2.1 (114)**	0.416 0.106 0.330
12 Months	**57.4 ± 1.3 (269)**	**54.6 ± 1.3 (248)**	**64.1 ± 1.6 (149)**	0.002** <0.001*** 0.125	**52.4 ± 1.5 (211)**	**51.5 ± 1.5 (199)**	**58.0 ± 2.1 (117)**	0.025* 0.010* 0.680
24 Months	**58.4 ± 1.5 (221)**	**52.6 ± 1.5 (222)**	**64.2 ± 1.9 (132)**	0.110 <0.001*** 0.006**	**50.6 ± 1.7 (194)**	**47.4 ± 1.9 (181)**	**55.7 ± 2.5 (101)**	0.086 0.009** 0.210
36 Months					**48.1 ± 1.8 (183)**	**46.1 ± 2.0 (177)**	**53.4 ± 2.7 (102)**	0.094 0.033* 0.486

Modified from tables 2.2.3A and 2.2.3B, OVERALL LONG-TERM RENAL FUNCTION SUMMARY, pages 45 and 49.

a: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. b: Number of patients used to calculate the mean.

Reviewer's comment:

Mean GFR values were significantly lower for both the 2-mg/day and 5-mg/day sirolimus cohorts than for the azathioprine group at months 6 and 12. At 24 months mean GFR for the AZA group was significantly better compared to the SRL5, and numerically superior to the SRL2 this comparison was only statistically significant for the 5-mg/day sirolimus group. GFR in the SRL 5 significantly decreases over time while the GFR in the AZA group remain stable from 6 to 12 months.

The values decreased from 6 to 24 months in the 5-mg/day sirolimus group but changed little over this interval in the 2-mg/day sirolimus and azathioprine groups. (see table 17.1-1)

S-302: Between 6 and 36 months, mean values for Nankivell GFR decreased in all 3 groups, although to a lesser extent for the placebo cohort than for the sirolimus cohorts. Mean GFRs were significantly lower than placebo in both sirolimus treatment groups at 12 months, but only in the 5-mg/day cohort at 24 and 36 months.

17.2. Long-term Renal Function Study 309

S-309 was a designed to test therapeutic equivalence between the oral solution and the tablet formulation. This study enrolled 477 patients randomly assigned (1:1) to receive CsA and corticosteroids with sirolimus (2 mg/day), administered either as the liquid or tablet formulation. ITT mean Nankivell GFR analysis for sirolimus liquid vs solid formulation showed a decreased in GFR over time in both the cohorts from 6 to 12 months. The decline in GFR over time was similar and no differences were detected between formulation groups. (See table 17.2-1)

Table 17.2-1. MEAN VALUES (± SEM) FOR CALCULATED NANKIVELL GFR (mL/min): 6 AND 12 MONTHS POSTTRANSPLANTATION: ITT ANALYSIS, STUDY 309

	Sirolimus Solution (2 mg/day)	Sirolimus Tablet (2 mg/day)	ANOVA p
Month 6	56.4±1.5	53.8±1.7	0.261
Month 12	53.1±1.7	51.7±1.7	0.578

Modified from table A2, page 66. OVERALL LONG-TERM RENAL FUNCTION SUMMARY

17.3. Slope Analyses Studies 301 and 302:

Table 17.3-1. ITT SLOPE ANALYSES FOR ANNUAL CHANGE IN NANKIVELL GFR (mL/min/year), S-301 AND S-302

Period (months)	*SRL2 + CsA*	*SRL5 + CsA*	*Control arm S-301 AZA or S-302 Placebo*	p-Value SRL 2 vs Control SRL 5 vs Control SRL 2 vs SRL 5
S-301, 6 to 24				**0.194**
Slope (mean±SEM)	**-3.5 ± 0.8**	**-3.1 ± 0.8**	**-1.8 ± 1.1**	**0.339**
95% CIs	**-5.1, -1.9**	**-4.7, -1.4**	**-3.9, 0.3**	**0.692**
p-Value	**<0.001*** **	**<0.001*** **	**0.099**	
# patients to calculate the mean	**275**	**253**	**151**	
S-302, 6 to 36				**0.118**
Slope(mean±SEM)	**-2.6 ± 0.5**	**-2.4 ± 0.6**	**-1.1 ± 0.7**	**0.165**
95% CIs	**-3.6, -1.5**	**-3.5, -1.3**	**-2.6, 0.3**	**0.847**
p-Value	**<0.001*** **	**<0.001*** **	**0.119**	
# patients to calculate the mean.	**209**	**200**	**114**	

Modified from tables 2.2.6.2A and 2.2.6.2A Overall Long-term Renal Function Summary, pages 54 and 56
A p-value <0.05 indicates that the negative slope is statistically different from zero. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Reviewer's comments: ***On-therapy and ITT slope analyses on S-301and S-302 showed a negative slope for the plots of $1/Sc_r$ versus time and GFR versus time. These results were consistent with deteriorating renal function over the intervals studied and statistically significant for the 2-mg/day and 5-mg/day sirolimus groups, but not for the comparator groups.*** (See table 17-3-1)

17.4. Long-term Renal Function Extension Study 311

S-311 is a multicenter, extension study being conducted in
Australia, Canada, Europe, and New Zealand for the purpose of accumulating long-term safety data from patients who participated in clinical trials involving the use of sirolimus for prophylaxis of acute solid organ (kidney, heart, or liver) transplant rejection.
The applicant presented data from renal transplant patient on long term renal function.

Reviewer's comment: ***On therapy Slopes of calculated GFR from 6 to 36 months showed better glomerular filtration rate in renal allograft recipients receiving sirolimus without calcineurin inhibitor therapy. Patients that receive the CsA+SRL combination experienced an approximately 3.5 mL/min/year decrease in GFR.***

17.5. REVIEWER'S SUMMARY AND CONCLUSIONS:

- ***The ITT and on-therapy analyses demonstrated better GFR among CsA withdrawn patients compared with patients who continued on CsA plus sirolimus combination (S-212 and S-310). We agree with the applicant that CsA withdrawal, in the populations studied, is associated with superior renal function through 36 months posttransplantation compared with the patients that continue on CsA + SRL combination.***

- ***The above difference between arms is significant and increase over time through 36 months posttransplantation. However, from 12 to 36 months the GFR remained practically unchanged in group B and the difference between arms is mainly due to GFR deterioration in the CsA + SRL arm.***
  After the initial improvement in GFR associated with CsA withdrawal (Removal of the afferent arteriole vasoconstrictive effect from CsA). The renal function in group B remains practically unchanged over time.

- ***Patients on the best baseline GFR quartile apparently reach GFR zenith earlier in time compared to other quartiles and the GFR decline became evident at 12 (-1.4 ml/min), 24 months (-3.5 ml/min) and 36 months (-4.1ml/min).***

- ***We agree with the sponsor that the findings from the studies 301, 302, and 309 and CsA withdrawal studies 310 and 212 (On therapy and ITTanalysis) corroborates that renal function decreases over time with a SRL+ CsA regimen suggesting a CsA-associated nephrotoxicity which is exacerbated by its co-administration with sirolimus. These findings were numerically and /or significantly more pronounced, for patients receiving the 5-mg/day dose of sirolimus than for those receiving the 2-mg/day dose of sirolimus suggesting a dose related effect on cyclosporine nephrotoxicity.***

18. LONG-TERM INFORMATION FROM STUDIES 301 AND 302

(24 and 36 months follow up, respectively)

The February 08, 2002, FDA-approvable letter asked the applicant to:

"Complete your postmarketing commitment to provide long-term information from studies 301 and 302, including intent-to-treat information on renal function, whether or not patients continued on study drug. The 24-month reports submitted for these studies have only included on-therapy analyses of renal function and therefore do not meet this postmarketing commitment. Include a slope intercept analysis of serum creatinine clearance as well."

This section of the review will address the long-term data on studies 301 and 302 on:

- Patient and graft survival.
- Causes for death.
- Infections and malignancies.
- Long-term data on acute rejection (Please see: **CHARACTERIZATION OF REJECTION PATTERNS IN STUDIES 301-US 302-GL AND 310-GL** and **IMPACT OF REJECTION ON RENAL FUNCTION)**
- Long-term data on renal function (Please see **ITT ANALYSES ON RENAL FUNCTION** and **IMPACT OF REJECTION ON RENAL FUNCTION).**

Phase III trials i.e. pivotal studies 301 and 302 were randomized, double blind, controlled trials. Study 301-US enrolled 719 patients and utilized azathioprine as an active control. Study 302-GL enrolled 576 patients and utilized a placebo control.
The main endpoints in both studies included a composite endpoint of acute rejection, graft loss or death at 6 months and patient and graft survival at 12 months. Table 18.1 summarizes the similitude and differences of these studies.

Table 18-1

Study	Primary endpoint	Time of Randomization	Stratification	Patients randomized	Time of evaluation	Groups** SRL and AZA Doses (n)	Sex & Race
301 US	*Efficacy failure within the first 6 months after transplantation	**24-48 hours Post-transplant 2:2:1 SRL 2: SRL 5: AZA**	**Investigator and Race**	**719**	**24 mo.**	**SRL 2mg/day (n=284) SRL 5mg/day (n=274) AZA 2-3mg/kg/day (n=161)**	**M=469** F=250 **W=406** **B=166** H=105 A=27 Other=15
302 AU, CA, EU, US		**Pre-transplant randomization 2:2:1 SRL 2: SRL 5: Placebo**	**Investigator and Donor Origin**	**576**	**36 mo.**	**SRL 2mg/day (n=227) SRL 5mg/day (n=219) Placebo (n=130)**	**M=388** F=188 **W=450** **B=66** A=20 H=12 AU=4 Other=24

*Efficacy failure was defined as the first occurrence of: 1) Biopsy-confirmed acute rejection, 2) graft loss (Physical or Functional (> 56days of continuous dialysis)) or 3) Death
** All groups received CsA and Corticosteroids

18.1. Patient and graft survival:

Table 18.1-1 summarizes data on graft survival at 24 and 36 months for patients enrolled in studies 301 and Study 302.
Graft survival was analyzed in both studies by the Kaplan-Meier method for the estimation of time to graft loss. Log-rank test assessment for the differences between treatment groups was not statistically significant in both S-301 and S-302.

Reviewer's comment: ***85/719(11.8%) and 109/576 (19%) patients in S-301 and 302, respectively loss their grafts during the follow up periods.***
Death with a functioning graft was the most common cause of graft loss in S-301 (34%) and 302 (40%), and across arms. Differences in graft loss among the treatment groups were not statistically significant (See table 2). Other causes for graft loss included renal artery or vein thrombosis, acute rejection, and ATN.

Table 18.1-1. ITT ANALYSIS OF GRAFT SURVIVAL AT 24 AND 36 MONTHS, STUDIES 301 AND 302, RESPECTIVELY

	Study 301 (24 months)			Study 302 (36 months)		
	SRL 2 mg/day (n=284)	SRL 5 mg/day (n=274)	AZA (n=161)	SRL 2 mg/day (n=227)	SRL 5 mg/day (n=219)	Placebo (n=130)
Graft survival, n (%)	**242 (85.2)**	**244 (89.1)**	**145 (90.1)**	**184 (81.1)**	**175 (79.9)**	**105 (80.8)**
Graft loss [a]	25 (8.8)	19 (6.9)	12 (7.5)	24 (10.6)	27 (12.3)	14 (10.8)
Patient death [b]	14 (4.9)	11 (4.0)	4 (2.5)	19 (8.4)	15 (6.9)	10 (7.7)
Lost to follow-up	3 (1.1)	**0**	**0**	**0**	2 (0.9)	1 (0.8)
Difference in rates (95% CI) [c]	-4.9 (-11.1 to 1.4)	-1.0 (-6.9 to 4.9)		0.8 (-8.2 to 8.8)	-0.9 (-9.5 to 7.8)	

a: Defined as functional graft loss (dialysis > 56 days), nephrectomy, or re-transplant.
b. Death with functioning graft.
c: Rate of graft survival in sirolimus group minus rate of graft survival in azathioprine group. A, difference > 0 is favorable to sirolimus.
Modified from **Overall long-term patient and graft survival, acute rejection, and serious adverse events summary,** tables 2.2.3A and 2.2.4A, pages 36 and 38.

Table 18.2-1 summarizes patient survival rates in S-301 and S-302 by treatment arms. Kaplan-Meier estimates of patient survival showed no significant differences between treatment groups for patient survival through 24 and 36 months by the log-rank test analysis.
At 24 months, there was no significant difference in patient survival between either sirolimus treatment group (2-mg/day or 5-mg/day) and the azathioprine group.

18.2 Patient survival and causes for death:

Table 18.2-1. ITT ANALYSIS OF PATIENT SURVIVAL CAUSES FOR DEATH AND LOST TO FOLLOW UP, STUDIES 301 AND 302, RESPECTIVELY.

	Study 301 (24 months)			Study 302 (36 months)		
	SRL 2 mg/day (n=284)	SRL 5 mg/day (n=274)	AZA (n=161)	SRL 2 mg/day (n=227)	SRL 5 mg/day (n=219)	Placebo (n=130)
Patient survival, n (%)	263 (92.6)	260 (94.9)	155 (96.3)	205 (90.3)	196 (89.5)	118 (90.8)
Difference in rates (95% CI)a.	-3.7 (-7.9 to 0.6)	-1.4 (-5.3 to 2.5)		-0.5 (-6.8 to 5.9)	-1.3 (-7.7 to 5.2)	
Death						
Infection	6 (2.1)	4 (1.5)	1 (0.6)	5 (2.2)	5 (2.3)	1 (0.8)
Cardiovascular events	3 (1.1)	4 (1.5)	0	9 (4.0)	6 (2.7	5 (3.9)
Malignancy	2 (0.7)	0	1 (0.6)	5 (2.2)	3 (1.4)	2 (1.5)
Miscellaneous	4 (1.4)	6 (2.2)	3 (1.9)	2 (0.9)	6 (2.7)	3 (2.3)
Total	15 (5.3)	14 (5.1)	5 (3.1)	21 (9.3)	20 (9.1)	11 (8.5)
Lost to follow-up	6 (2.1)	0	1 (0.6)	1 (0.4)	3 (1.4)	1 (0.8)

Modified from, **Overall long-term patient and graft survival, acute rejection, and serious adverse events summary, tables 2.3.3A, 2.3.3B, 2.3.4A and 2.3.4B pages 49, 50, 51 and 52, respectively.**
a. Rate of patient survival in sirolimus group minus rate of patient survival in azathioprine or placebo group. A difference > 0 is favorable to sirolimus.

18.3. Infections:

In S-301, the incidence of infection-related TEAEs were significantly different among groups, 71%, 66% and 53% groups SRL5, SRL2 and Aza, respectively.
Infection-related TEAEs such as Herpes simplex virus (HSV), pneumonia (excluding opportunistic infections), bronchitis, Upper respiratory infection and pyelonephritis were significantly higher in the SRL-5 than SRL-2 or Aza.
Four patients presented severe HSV (3 in the SRL-5 and one in the Aza groups). One patient in the SRL-5 was discontinued for this reason. Table 18.3-1. summarizes the infection-related TEAEs in S-301

Table 18.3-1. NUMBER (%) OF PATIENTS REPORTING TREATMENT-EMERGENT ADVERSE EVENTS RELATED TO INFECTION ≥5% STUDIES 301

	Study 301 (24 months)		
	SRL 2 mg/day (n=281)	SRL 5 mg/day (n=269)	AZA (n=160)
Infections a.	185 (65.8%)	191 (71.0%)	85 (53.1%)
Pneumonia b.	24 (8.5)	34 (12.6)	7 (4.4)
Upper respiratory infection b.	50 (17.8)	62 (23.0)	18 (11.3)
Herpes simplex b.	12 (4.3)	37 (13.8)	5 (3.1)
Severe HSV infections b.	0	3(1%)	1(<1%)

Modified from, Overall long-term patient and graft survival, acute rejection, and serious adverse events summary, tables 2.4.3A.page 63.

a. Excluding opportunistic pneumonia.

b. The difference between treatment groups was statistically significant

Reviewer's comment: ***These are infections reported as TEAEs without necessarily bacteriologic or virologic confirmation and result should be interpreted with caution. However, one cannot exclude a dose related effect. The 5 mg dose appears to be less optimal with respect to infections.***

Table 18.3-2. summarizes the rates for selected clinically important infections. Higher rates are bolded.

Table18.3-2. INCIDENCE RATES FOR SELECTED CLINICALLY IMPORTANT INFECTIONS AT 24 AND 36 MONTHS STUDIES 301 AND 302, RESPECTIVELY.

	Study 301 (24 months)			Study 302 (36 months)		
	SRL 2 mg/day (n=281)	SRL 5 mg/day (n=269)	AZA (n=160)	SRL 2 mg/day (n=227)	SRL 5 mg/day (n=219)	Placebo (n=130)
Pneumonia a.	22 (7.7)	**26 (9.5)**	9 (5.6)	**27(11.9)**	20(9.1)	10(7.7)
Pneumocystis carinii pneumonia	2 (0.7)	1 (0.4)	0	0	0	1
CMV infection a (generalized)	11 (3.9)	9 (3.3)	7 (4.3)	12(5.3)	**20(9.1)**	8(6.2)
CMV infection (tissue-invasive)	4 (1.4)	5 (1.8)	5 (3.1)	7(3.1)	**10(4.6)**	2(1.5)
Sepsis	25 (8.8)	24 (8.8)	10 (6.2)	16(7.1)	**27(12.3)**	10(7.7)
Wound Infection	19 (6.7)	25 (9.1)	7 (4.3)	21(9.3)	**27(12.3)**	12(9.2)
UTI / pyelonephritis	64 (22.5)	71 (25.9)	53 (32.9)	73(32.2)	**81(37.0)**	34(26.2)

Modified from, Overall long-term patient and graft survival, acute rejection, and serious adverse events summary, tables 2.4.3B and 2.4.4A.pages 63-64 and 65-66 respectively.

a. Excluding opportunistic pneumonia.

b. In S-301, infection incidence is reported as related TEAEs during the "on treatment" status of the patients.

c. For S-302 ITT analysis of infection rates was done on 36-month data.

In S-301 the incidence rates of HSV infection and pneumonia in patients treated with sirolimus 5 mg/day were higher than those in patients treated with either sirolimus 2 mg/day or with azathioprine. One (1) patient in the sirolimus 5-mg/day group was withdrawn because of severe HSV infection.

Reviewer's comment: ***UTI was the most common infection among all treatment arms in S-301 and 302 ITT populations.***
Herpes simplex was significantly higher in SRL-5 arm than the SRL-2 control groups in S-301. Similarly, in S-302 Herpes simplex incidence was significantly higher in SRL-5 compared to SRL-2 or placebo.
Wound infection was numerically higher in SRL-5 arm than the SRL-2 and control groups in both S-301 and 302.
Pneumonia was a common infection among S-301 and S-302 and across arms. It was numerically higher in SRL-5 and SRL2 in studies S-301 and S-302, respectively.
Sepsis occurred at a similar rate across the treatment groups.

18.4. Malignancies:

In S-301, 33 malignancies were reported. Six (6) cases of PTLD and lymphoma were reporter (0.7%, 1.1% and 0.6% groups SRL2, SRL5 and Aza respectively) and there were no statistically significant differences between sirolimus groups and the azathioprine group.
In S-302, fifty-three (53) malignancies were reported. 12 patients developed PTLD/Lymphoma.

Table 18.4-1. INCIDENCE RATE OF MALIGNANCIES AT 24 AND 36 MONTHS STUDIES 301 AND 302, RESPECTIVELY

	Study 301 (24 months) a, b			Study 302 (36 months) a, b		
	SRL 2 mg/day (n=281)	SRL 5 mg/day (n=269)	AZA (n=160)	SRL 2 mg/day (n=227)	SRL 5 mg/day (n=219)	Placebo (n=130)
PTLD/Lymphoma	0.7	1.1	0.6	1.8	3.2	0.8
Skin Carcinoma total	1.1	3.3	4.3	4.4	4.1	7.7
Any Squamous Cell c. (%)	0.4	2.2	3.8	2.7	0.9	3.0
Any Basal Cell c.	0.7	1.5	2.5	2.2	1.8	5.3
Melanoma	0	0	0	0.4	1.4	0
Miscellaneous/Not Specified	0	0	0	0	0	0.8
Other Malignancy	1.1	1.5	0.6	2.2	1.4	2.3

Modified from, **RESPONSE TO FDA REQUEST FOR INFRMATION DURING LABELING NEGOCIATIONS.**
a. All patients received corticosteroids
b. Includes discontinued patients
c. **Patients may be counted in more than one category**

In study 301, the rate of malignancy was numerically lower in the SRL-2 group (2.8%) as compared to both SRL-5 group (5.8%) and Aza group (5.6%). The incidence of PTLD was similar in all 3 groups.
In study 302, the overall incidence of malignancy was similar across treatment arms (8.4% to 10.8%). PTLD/lymphoma was numerically higher in the SRL-5 group (3.2%) than either the SRL-2group (1.8%) or placebo group (0.8%).
Skin carcinomas were more frequent (7.7%) in the placebo group. (See **Table 18.4-1.**)

Reviewer's comment: ***Squamous and basal cell carcinoma were the most frequently reported malignancies. Basal cell carcinoma represents the least aggressive of all non-melanoma skin cancers and is successfully treated. On the other hand hand Squamous cell carcinomas (SCCs), were more frequent in group***

18.5. REVIEWER'S SUMMARY AND CONCLUSIONS:

- ***Graft survival ranged from 85% to 90% in S-301 (24 months) and from 80% to 81% in S-302 (36 months). There was no significant difference in the rate of graft survival between the three groups.***
- ***Death with a functioning graft was the most common cause of graft loss (34% and 40%, of all graft losses in S-301 and 302, respectively)***
- ***Patient survival in studies 301 and 302 showed no statistically significant difference across the treatment groups in both studies.***
- ***The most common causes of death were due to infection and cardiovascular events in both S-301 and 302.***
- ***In S-302, the incidence of patient death was similar among treatment groups. In contrast, in S-301 a lower rate of patient death were observed in the Aza arm (control group) and the overall rates observed in each group, were almost half of those observed in their homologous arms in S-302.***
- ***UTI was the most common infection among all treatment arms in S-301 and 302 ITT populations.***
- ***Pneumonia, and Wound infection were numerically higher in SRL-5 than control groups in both S-301 and 302.***
- ***Herpes simplex was significantly higher in SRL-5 arm than the SRL-2 control groups in S-301. Similarly, in S-302 Herpes simplex incidence was significantly higher in SRL-5 compared to SRL-2 or placebo.***
- ***The differences in the incidence of malignancies between either sirolimus dose group or the control groups was not statistically significant in both S-301 and S-302 (See table 6)***

19. THERAPEUTIC DRUG MONITORING RECOMMENDED RANGE

FDA post-approval requirement:
"The appropriate study(ies) will be conducted to evaluate the effect of ethnicity on the PK 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 PK analysis, preferably using mixed effects modeling".

February 8, 2002 FDA-approvable letter action items:
"Define a therapeutic concentration range for sirolimus therapeutic drug monitoring in renal transplant patients whose cyclosporine has been eliminated by providing data and analyses that support this range and identifies the efficacious and maximum tolerated (safe) concentrations".

July 29, 2002 pre-NDA meeting action items:
" Rationale for Wyeth proposed TDM scheme"

The maximum tolerated concentration range for sirolimus-based maintenance therapy after CsA withdrawal was evaluated in the CsA elimination studies (S-310 and S-212). In the pivotal study 310, sirolimus concentrations ranged from 15 to 30 ng/mL (12 to 24 ng/mL by chromatographic methods). Supportive study 212 explored lower sirolimus levels after CsA elimination (10-20 ng/mL measured by immunoassay).
The data from both studies support the safety and effectiveness of these concentrations in the Rapamune® Maintenance Regimen (RMR) when CsA is withdrawal. Therefore, the trough whole blood sirolimus concentration (12 to 24 ng/mL by chromatographic method) proposed by the sponsor is an acceptable target range.

Please refer to the Clinical Pharmacology and Biopharmaceutics review for the in depth review of the applicant's response

NDA 21-083/S-006
NDA 21-110/S-004

20. WYETH'S JUSTIFICATION FOR NOT WAITING FOR RE-SUBMISSION UNTIL STUDIES 316 AND 101164 ARE COMPLETED

At the pre-submission meeting held on July 29, 2002:

"The Agency agreed with the applicant's overall plan for submitting a response to the February 8, 2002 letter; however, Wyeth agreed to submit a thorough justification for not waiting until Studies 316 and 101164 are complete. ***It is customary for a response to an approvable letter to be a complete response. However, because studies 0468H1-316-GL (renal conversion study) and 0468H1-101164-US (high-risk study) will not be complete for several years, Wyeth should provide a justification of the appropriateness to resubmit now, rather than await the completion of these studies".***
The study description was copied from the applicant's justification and status report on S-316 and S-101164.

Study 0468H1-316-GL (renal conversion study) is being conducted at approximately 80 centers in Australia, Canada, Europe, and North America, with a planned enrollment of approximately 750 patients over a 1-year period. Eligible patients are those who are 6 to 60 months posttransplantation, with stable or slowly deteriorating renal function, and who have been receiving a calcineurin inhibitor (CsA or tacrolimus)-based, triple immunosuppressive drug regimen.

The first patient was randomly assigned in study 316 on 05 Feb 2002. As of 19 Aug 2002, 153 patients had been randomly assigned at 38 centers globally: 75 in the United States (US), 77 in the European Union (EU), and 1 in Canada.

The approximate target date for completion of enrollment is first quarter of 2003. The target for completion of 12 months of randomized treatment by the 750th patient is first quarter 2004. Subsequently, filing will occur with 1-year data.

Study 0468H1-101164-GL(high-risk patients study) is an open-label, concentration-controlled, randomized, 12-month study of tacrolimus + sirolimus + corticosteroids compared to cyclosporine + sirolimus + corticosteroids in high-risk renal allograft recipients. This study is designed to show that when compared to patients treated with sirolimus and cyclosporine, patients treated with sirolimus and tacrolimus will demonstrate:

- Non-inferiority of the rate of efficacy failure at 12 months, defined as the first episode of biopsy confirmed acute rejection, graft loss, or death, in the intent-to-treat population.
- Superiority with respect to renal allograft function at 12 months. Approximately 460 patients at 30 centers will be randomized 1:1 to receive sirolimus and corticosteroids in combination with either tacrolimus or cyclosporine.

As of 06 Sep 2002, 12 centers have been initiated and 7 patients have been enrolled. The approximate target date for completion of enrollment is 2nd quarter 2004 with 12-month follow-up data available 2nd quarter 2005. Submission of the 12-month study report will occur in the 4th quarter 2005.

Reviewer's Comment: FDA agreed to accept an incomplete response to the February 08, 2002 FDA-approvable letter and review the Wyeth's resubmission for **"Rapamune Maintenance Regimen Following Cyclosporine Withdrawal in Renal Allograft Recipients"** *The decision was based on:*

- *24- months results from the pivotal S-310 showed adequate patient, graft survival and superior renal function over time in the CsA withdrawal arm compared with the CsA + SRL combination. These results were considered relevant for the potential benefit of the proposed indication to a large sub-population of renal allograft recipients.*
- *Three year data analysis on S-310, further suggest a tendency to better renal function and non inferior graft survival compared with the SRL + CsA combination which showed renal function deterioration over time. Therefore, because of these relevant findings; the applicant has decided to offer the RMR to all patients enrolled in the CsA + SRL arm. The FDA strongly agree with this decision providing that study data will collected up to 5 years as originally planed.*

- *Findings from the studies 301, 302, and 309 and CsA withdrawal studies 310 and 212 (On therapy and ITT analysis) corroborates that renal function decreases over time with a SRL+ CsA regimen suggesting a CsA-associated nephrotoxicity which is exacerbated by its co-administration with sirolimus.*

- *According to the characteristics of US renal transplant population and taking into consideration the inclusion / exclusion criteria used in the S-310 and S-212 we can conservatively assume that more than 50% of the US renal transplant patients would be eligible for the proposed regimen.*

- *It remains to be seen whether RMR with CsA withdrawal is appropriate beyond 4 months posttransplantation. The "renal conversion study" S-316-GL will elucidate this concern.*

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/s/

Arturo Hernandez
4/18/03 04:29:04 PM
MEDICAL OFFICER

Arturo Hernandez
4/18/03 04:31:31 PM
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NDA 21-083/S-006 and 21-110/S-004

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4/18/03 04:35:00 PM
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4/24/03 11:18:24 AM
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INTEGRATED REVIEW OF SAFETY

Rapamune® (Sirolimus)

Cyclosporine Withdrawal in Renal Transplantation

NDA 21-083 /SE 1-006
NDA 21-011/ SE 1-004

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Introduction

The basis of the initial 1999 approval of Rapamune® (sirolimus) for the prevention of acute rejection in renal transplantation included two randomized, double-blind, phase III studies (301 and 302) comparing Rapamune®, 2 mg and 5 mg, to azathioprine or placebo. Both studies demonstrated the non-inferiority of Rapamune® with respect to 12-month patient and graft survival, and a significant reduction in the incidence of rejection at 6 months. Despite a lower rate of acute rejection at 6 months post-transplantation, renal function, as measured by serum creatinine and calculated glomerular filtration rate (Nankivell GFR method), was decreased at 12 months in the sirolimus treatment groups compared to controls.

As a phase 4 commitment, the Applicant agreed to report long term follow-up safety and efficacy data from studies 301 and 302. It was requested that data pertaining to GFR and serum creatinine be included as follow-up information and be collected throughout the entire duration of the study whether or not patients remained on study drug. Based on 24- month data, of only those patients who remained on assigned therapy, renal function continued to be decreased in the Rapamune® treatment groups compared to controls.

It had been noted in the double-blind studies, 301 and 302, that mean and median whole blood cyclosporine (CsA) concentrations had remained at or above the upper limit of the specified target concentration ranges. Therefore, an additional commitment was to evaluate the optimum therapeutic range for sirolimus and the value of reduced cyclosporine concentrations in combination with sirolimus. Proposed sirolimus concentration ranges were based on preliminary pharmacokinetic / pharmacodynamic analyses on a subset of patients in the phase III studies. The sirolimus concentration ranges were evaluated prospectively in the subsequent controlled studies included in this NDA.

The Applicant is now proposing to amend the labeling to include a consideration of cyclosporine withdrawal at 2 to 4 months after transplantation and the use of concentration-controlled sirolimus adjusted to 15 to 25 ng/mL (by immunoassay) when used without cyclosporine.

The application for this labeling change is supported by the two clinical studies described below.

Pivotal study 310 was an open label, non-IND study done in Europe, Canada and Australia with randomization at month 3 post- transplant. Study 310 excluded high risk transplant recipients from randomization to cyclosporine maintenance or withdrawal at 2 to 4 months after transplantation, based on protocol specified exclusion criteria: Banff Grade III acute rejection episode or vascular rejection 4 weeks before random assignment; dialysis dependency, serum creatinine > 400 μmol/L or inadequate renal function (in the opinion of the investigator) to support CsA elimination. Few study patients were excluded based only on "physician's judgment".

Supportive study 212 was an open-label study done in the US and Europe with randomization done at an earlier time than in study 310 i.e. at days 2 to 7 post-transplant. Early randomization at 2-7 days post- transplant in study 212 allowed for drop-out before reaching the time of cyclosporine withdrawal. Patients with adequate renal function (as determined by the investigator) were randomly assigned, within 48 hours after transplantation, to cyclosporine maintenance or withdrawal. The remaining patients were eligible for randomization if their acute tubular necrosis (ATN)/ delayed graft function (DGF) had resolved sufficiently by the 7th day to allow them to receive cyclosporine A. Patients whose ATN/DGF had not resolved by day 7 after transplantation were not randomized.

In the cyclosporine withdrawal arm of both clinical studies, the dosage of sirolimus increased after cyclosporine withdrawal and was adjusted to maintain whole blood concentrations by immunoassay. In study 310, the targeted sirolimus trough levels were higher at 20-30 ng/ml; while in study 212, the targeted sirolimus trough levels were 10 to 20 ng/ml.

The strengths of these two studies included the randomized controlled design, the quality of cyclosporine concentration-control, the quality of sirolimus concentration-control and the quality of follow-up for patient and graft survival and renal function.

Weaknesses of the studies included the open-label study design which creates a potential for bias in the assessment of acute rejection episodes or comparative safety. The lack of adequate representation of United States sub-populations of interest such as African-Americans and Hispanic patients was another study weakness.

Overall, we are in general agreement with the Applicant's description of these studies and the reported results.

A. Brief Statement of Conclusions

The focus of the safety review was to evaluate:

1) whether the rates of rejection and graft survival were equivalent when one spares cyclosporine and uses a higher concentration of sirolimus compared to standard cyclosporine regimens
2) whether the study population in the cyclosporine-sparing arm truly experienced less cyclosporine toxicity and
3) whether the benefits of less cyclosporine outweigh any risks associated with increased sirolimus exposure.

In addition, it was important to attempt to identify the population of renal transplant recipients that could most benefit from a sirolimus concentration-controlled and cyclosporine-sparing regimen.

Major toxicities that had already been identified for Rapamune® in the original NDA included: thrombocytopenia, leukopenia, hyperlipidemia and elevated GFR and serum

creatinine. Post-marketing concerns have included reports that patients on Rapamune® may develop a pneumonitis/pneumopathy that appears to be non-infectious and resolves with discontinuation of Rapamune®.

Safety

We agree with the Applicant that patients in the cyclosporine-sparing/ sirolimus concentration-controlled arm experienced less cyclosporine-related toxicities such as hypertension, hyperuricemia and edema. In the cyclosporine-sparing/ sirolimus concentration-controlled arm, significantly better renal function at 12 months as measured by GFR and serum creatinine was noted in both studies. However, whether this improved renal function will be sustained at 24 months still must be determined (see phase 4 commitments below). It was also recommended that additional studies could be done to more precisely identify the most safe and efficacious dose ranges for sirolimus.

In study 310, elevated ALT was reported more frequently reported in the concentration-controlled sirolimus group. In study 212, diarrhea and atrial fibrillation were reported more frequently in the concentration-controlled sirolimus group. In addition, in both studies, patients in the cyclosprorine-sparing /sirolimus concentration-controlled arm did more commonly develop thrombocytopenia, hypokalemia and liver function test abnormalities that may be due to greater Rapamune® exposure. These adverse events appear to be toxicities that the clinician can identify and manage. There were no major problems with bleeding or hepatic failure. No patient compliance issues or new sirolimus-related toxicity issues have been identified to date.

Efficacy

Overall, in terms of efficacy, it appears that the "price" of a cyclosporine-sparing, sirolimus concentration-controlled regimen appears is an increase in early mild-to-moderate acute rejection. However, this excess in acute rejection was not associated with a detectable decrease in patient or graft survival in the Rapamune® /cyclosporine withdrawal arm at 12 months after transplantation. In addition, there were no major differences in the treatment arms with regard to infection or malignancy that may have occurred because of anti-rejection therapy.

Additional issues that need to be addressed prior to approval include the need to:
-more precisely define the renal transplant population that can safely use a cyclosporine-sparing, sirolimus concentration-controlled regimen
-ensure that a feasible, reproducible therapeutic drug monitoring assay is available for patients on concentration-controlled sirolimus and identify the minimal trough level that can be utilized for efficacy and the maximum trough level that can be tolerated for safety
-demonstrate improved renal function in the 24 month intent to treat (ITT) renal function analyses in studies 310 and 212.

Approvability

After completing the review of these applications, the indication for use of Rapamune® in a cyclosporine withdrawal regimen was considered to be "approvable". This action was supported by the January 24, 2002 Advisory Committee member comments

regarding the need to determine the optimal sirolimus dose and method of therapeutic drug monitoring (TDM) and to identify the renal transplant population who will most benefit from using this sirolimus concentration-controlled and cyclosporine-sparing regimen. At the Advisory Committee meeting, members also suggested that the Applicant explore/evaluate a regimen of concentration-controlled sirolimus in combination with a minimal level of cyclosporine rather that completely withdrawing the cyclosporine.

B. Description of Patient Exposure

Demographics and Underlying Disease

Table 1* Study 310 Demographic and Baseline characteristics for RENAL ALLOGRAFT RECIPIENTS ITT POPULATION: STUDY 310

Characteristic	RAPA + CsA (n = 215)	RAPA (n = 215)	RAPA + CsA vs RAPA p-Value	Nonrandomized (n = 95)	Total (n = 525)
Sex, n (%)			0.314[a]		
Female	72 (33)	82 (38)		35 (37)	189 (36)
Male	143 (67)	133 (62)		60 (63)	336 (64)
Ethnic origin, n (%)			0.689[a]		
White	201 (93)	205 (95)		90 (95)	496 (94)
Black	5 (2)	2 (<1)		1 (1)	8 (2)
Asian	4 (2)	3 (1)		3 (3)	10 (2)
Other	5 (2)	5 (2)		1 (1)	11 (2)
Age, years			0.317[b]		
Mean	45.8	44.6		48.8	45.9
Standard deviation	11.6	13.1		13.5	12.7
Minimum	16	16		21	16
Maximum	68	73		72	73
Median	47.0	45.0		52.0	47.0
Height, cm	(n = 208)[c]	(n = 207)[c]	0.135[b]	(n = 92)[c]	(n = 507)[c]
Mean	169.6	168.1		168.7	168.8
Standard deviation	10.3	9.1		9.4	9.7
Minimum	135	142		145	135
Maximum	196	198		191	198
Median	170.0	169.0		170.0	169.0
Weight, kg			0.001[b]	(n = 95)[c]	
Mean	70.5	66.5		73.6	69.4
Standard deviation	13.8	12.6		16.0	14.0
Minimum	42	38		44	38
Maximum	139	104		110	139
Median	70.0	65.2		73.2	68.6
Number of HLA mismatches		(n = 214)[c]	0.525[b]		(n = 524)[c]
Mean	2.9	3.0		2.9	2.9
Standard deviation	1.4	1.3		1.5	1.3
Minimum	0	0		0	0
Maximum	6	6		6	6
Median	3.0	3.0		3.0	3.0

*From the Applicant's January 2002 Advisory Committee Briefing Package and please see Table 2 for a definition of the superscipts.

Medical Officer Comments: ***In study 310, there were no major imbalances across the treatment arms with regard to sex, ethnicity, age, height and number of HLA mismatches. Patients in the Rapamune®/cyclosporine (RAPA+ CsA) arm tended to have higher body weights than patients in the Rapamune® /cyclosporine withdrawal arm (RAPA).***

Table 2* Study 310 Demographic and Baseline Characteristics

RENAL ALLOGRAFT RECIPIENTS' ITT POPULATION: STUDY 310

Characteristic	RAPA + CsA (n = 215)	RAPA (n = 215)	RAPA + CsA vs RAPA p-Value	Nonrandomized (n = 95)	Total (n = 525)
Transplant, n (%)		(n = 214)[c]	0.603[a]		
Primary	197 (92)	193 (90)		83 (87)	473 (90)
Secondary	18 (8)	21 (10)		12 (13)	51 (10)
CMV status, n (%)	(n = 214)[c]	(n = 212)[c]	0.866[a]		
Negative	59 (28)	60 (28)		36 (38)	155 (30)
Positive	155 (72)	152 (72)		59 (62)	366 (70)
Primary etiology, n (%)			0.749[a]		
Autoimmune disease	2 (<1)	5 (2)		3 (3)	10 (2)
Diabetes mellitus	14 (7)	17 (8)		11 (12)	42 (8)
Failure of previous graft	2 (<1)	3 (1)		3 (3)	8 (2)
Glomerulonephritis	49 (23)	44 (20)		30 (32)	123 (23)
Hypertension	15 (7)	11 (5)		6 (6)	32 (6)
IgA nephropathy (Berger's)	25 (12)	29 (13)		9 (9)	63 (12)
Interstitial nephritis/pyelonephritis	16 (7)	19 (9)		7 (7)	42 (8)
Obstructive uropathy/reflux	8 (4)	8 (4)		7 (7)	23 (4)
Other/unknown	53 (25)	59 (27)		7 (7)	119 (23)
Polycystic disease-kidney	31 (14)	20 (9)		12 (13)	63 (12)
Delayed graft function,[d] n (%)	47 (21.9)	41 (19.1)	0.473[a]	46 (48.4)	134 (25.5)
Acute graft rejection,[e] n (%)	20 (9.3)	22 (10.2)	0.831[f]	27 (28.4)	69 (13.1)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CMV = cytomegalovirus, HLA = human leukocyte antigen, IgA = immunoglobulin A.

a: Pearson chi-square test.

b: Analysis of variance (ANOVA) with treatment as factor.

c: Where the values for n differ from the total number of patients in the groups, they are provided (for height, number of HLA mismatches, transplant, and CMV status for each group).

d: Delayed graft function: patient required dialysis for ≤ 8 days after transplantation.

e: Prerandomization rejection for all groups.

f: Fisher's exact test.

*From the Applicant's January 2002 Advisory Committee Briefing Package

Medical Officer Comments: ***In study 310, there were no major differences across the treatment arms in terms of the renal transplant recipient's cytomegalovirus (CMV) serologic status, whether the patient was a primary or secondary transplant, the occurrence of delayed graft function or acute rejection, and the primary etiology of underlying renal dysfunction.***

Table 3* Study 212 Demographic and Baseline Characteristics

RENAL ALLOGRAFT RECIPIENTS (ITT POPULATION): STUDY 212

Characteristic	RAPA + CsA (n = 97)	RAPA (n = 100)	p-Value[a]	Nonrandomized (n = 49)	Total (n = 246)
Sex, n (%)			0.852[b]		
Female	42 (43)	42 (42)		19 (39)	103 (42)
Male	55 (57)	58 (58)		30 (61)	143 (58)
Ethnic origin, n (%)			0.245[b]		
White	71 (73)	80 (80)		31 (63)	182 (74)
Black	18 (19)	15 (15)		14 (29)	47 (19)
Oriental (Asian)	4 (4)	2 (2)		1 (2)	7 (3)
Hispanic	1 (1)	3 (3)		3 (6)	7 (3)
Other	3 (3)	0		0	3 (1)
Age, years			0.839[c]		
Mean	44.9	45.2		47.8	45.6
Standard deviation	12.9	11.7		12.8	12.4
Minimum	19	20		19	19
Maximum	69	71		75	75
Median	46.0	47.0		48.0	46.5
Height, cm	(n = 96)[d]	(n = 96)[d]	0.159[c]	(n = 48)[d]	(n = 240)[d]
Mean	168.3	170.4		168.9	169.3
Standard deviation	10.8	9.5		10.3	10.2
Minimum	145	148		146	145
Maximum	191	193		191	193
Median	166.0	170.0		169.5	168.5
Weight, kg	(n = 95)[d]		0.857[c]		(n = 244)[d]
Mean	73.4	73.0		74.2	73.4
Standard deviation	16.8	17.1		18.9	17.3
Minimum	43	45		48	43
Maximum	128	123		113	128
Median	72.3	69.8		72.5	70.9
Recipient CMV status, n (%)		(n = 99)[d]	0.650[b]		(n = 245)[d]
Positive	61 (63)	68 (69)		32 (65)	161 (66)
Negative	19 (20)	15 (15)		10 (20)	44 (18)
Not done	17 (18)	16 (16)		7 (14)	40 (16)
Number of HLA mismatches, n (%)			0.329[b]		
0 to 3	60 (62)	55 (55)		24 (49)	139 (57)
4 to 6	37 (38)	45 (45)		25 (51)	107 (43)

*From the Applicant's January 2002 Advisory Committee Briefing Package

Medical Officer Comments: ***In study 212, there were no major imbalances across the treatment arms with regard to sex, ethnicity, age, height, weight, cytomegalovirus (CMV)serologic status of the renal transplant recipient and number of HLA mismatches.***

Table 4* Demographic and Baseline Characteristics

RENAL ALLOGRAFT RECIPIENTS (ITT POPULATION): STUDY 212

Characteristic	RAPA + CsA (n = 97)	RAPA (n = 100)	p-Value[a]	Nonrandomized (n = 45)	Total (n = 246)
Primary etiology, n (%)			0.684[b]		
Autoimmune disease	2 (2)	2 (2)		2 (4)	6 (2)
Diabetes mellitus	9 (9)	8 (8)		13 (27)	30 (12)
Glomerulonephritis	19 (20)	30 (30)		13 (27)	62 (25)
Hypertension	19 (20)	16 (16)		11 (22)	46 (19)
IgA nephropathy (Berger's)	9 (9)	8 (8)		1 (2)	18 (7)
Interstitial nephritis/ pyelonephritis	5 (5)	3 (3)		2 (4)	10 (4)
Obstructive uropathy/reflux	6 (6)	9 (9)		3 (6)[c]	18 (7)
Other/unknown	14 (14)	8 (8)		0	22 (9)
Polycystic disease-kidney	14 (14)	16 (16)		4 (8)	34 (14)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CMV = cytomegalovirus, HLA = human leukocyte antigen, IgA = immunoglobulin A.

a: p-Value compares RAPA + CsA with RAPA.

b: Pearson chi-square test.

c: Analysis of variance (ANOVA) with treatment as factor.

d: Where the values for n differ from the total number of patients in the groups, they are provided (for height, weight, and CMV status for each group).

e: One (1) patient in the nonrandomized group had a primary diagnosis of hydronephrosis, categorized in this table as obstructive uropathy.

*From the Applicant's January 2002 Advisory Committee Briefing Package

Medical Officer Comments: ***In study 212 there were numerically more cases of glomerulonephritis in the Rapamune®/cyclosporine withdrawal arm (RAPA).***

Advisory Committee members commented that studies 310 and 212 enrolled relatively fewer Black and Hispanic patients when compared to White patients. This does not adequately represent the US population currently on the waiting-list for a renal transplant. In addition, renal transplants from living vs cadaver donors are occurring more frequently. Study 310 enrolled only 8-9% recipients of living related (LRT) and 3% living unrelated renal transplants (LURT)and this does not reflect the trend toward more living donations.

Overall, there were no major demographic imbalances across the treatment arms in either study. Adequate numbers of female patients were enrolled. The youngest patient enrolled in studies 310 and 212 was 16 years of age. Most patients had 0 to 3 HLA mismatches and were seropositive for cytomegalovirus and thus at lower risk to develop invasive CMV disease.

Pharmacokinetics

Medical Officer Comments: ***The following information is taken from the Clinical Pharmacology review and please see this review for additional details.***

Background

Rapamune (sirolimus, Rapamycin) 1 mg/mL oral solution and 1 mg tablets were previously approved under NDA 21-083 and 21-110, respectively. Sirolimus is an immunosuppressive agent. It is a macrocyclic lactone produced by the fermentation of Streptomyces hygroscopicus. It is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone and acetonitrile.

Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-5) stimulation. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. This complex binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle.

This supplemental New Drug Application (sNDA) contained data to support a Rapamune Maintenance Regimen (RMR) in which Cyclosporine (CsA) is eliminated from the maintenance regimen after 2-4 months of triple immunosuppressive therapy of sirolimus, CsA and corticosteroids. Trough sirolimus concentration profiling was conducted in studies in order to 1) characterize the pharmacokinetic behavior of sirolimus during concomitant administration with CsA and corticosteroids and after withdrawal of CsA from the regimen and 2) to determine the therapeutic window of sirolimus during a maintenance regimen after withdrawal of CsA. Sirolimus (Rapamune®) is currently approved for prophylaxis of organ rejection in patients receiving renal transplants. Currently, it is recommended that Rapamune be used in a regimen with CsA and corticosteroids and it is taken at a fixed dose.

Medical Officer Comments: ***The Clinical Pharmacology staff believe that the Applicant has demonstrated that therapeutic drug monitoring is feasible for sirolimus. Mean (%CV) sirolimus trough concentration was 10.8 (36) ng/mL during concomitant administration with CsA and corticosteroids and 23.3 (22) ng/mL when CsA is eliminated from the regimen. The studies showed that a concentration range of 15 to 30 ng/mL (measured by immunoassay) may be an adequate concentration range for patients whose CsA has been eliminated from the regimen. Higher doses of sirolimus were needed to maintain the concentration range.***

This supplemental NDA for Rapamune maintenance regimen is for elimination of CsA after 2 –4 months of triple therapy. However, the data submitted did not allow evaluation of an exposure-response analysis after the patients were randomized to the CsA elimination arm of the therapy

[redacted]

[redacted]

Medical Officer Comments: The analytical methods were validated and considered to be acceptable by our FDA Clinical Pharmacology staff. These analytical methods have been used in other studies involving sirolimus and CsA. They were submitted and reviewed in NDA s 21-083 and 21-110.

T[redacted]not currently available. Blood samples have to be shipped to specific laboratories for analysis and results reported to the clinician. The turn around time could be a rate-limiting step in the expeditious and timely application of therapeutic drug monitoring (TDM) for sirolimus.

Exposure

Mean trough concentrations for sirolimus following 2 mg and 5 mg doses in the original NDA study 301 are depicted in Table 5 below. Note that the observed sirolimus trough concentrations in the current study 310 in the sirolimus concentration-controlled arm are comparable to those observed in the 5 mg arm of original NDA 21-083 study 301.Trough concentrations were determined using an immunosassay method in the clinical trials. The Applicant is proposing a validated HPLC methodology for the therapeutic dose monitoring This involves sending samples to analytical centers (laboratories) for determining the trough concentrations.

Table 5* Mean Sirolimus Trough Concentrations (ng/ml)

Study	Dose	Mean ± SD (n)	Range
301	2 mg	8.59 ± 4.01 (226)	4.5 - 14
301	**5 mg**	**17.3 ± 7.35 (219)**	**10.0 - 28**
310	2 mg	10.8 ± 3.9 (204)	6.5 - 15
310 (no CsA)	**TDM dosing**	**23.3 ± 5.1 (200)**	**16.9 - 29.6**

*from FDA Advisory Committee presentation January 2002

Medical Officer Comments: The clinical pharmacology staff concluded that based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21-083 SE1-006 to fulfill section 320 and 201.5 of 21 CFR, the target trough concentration for sirolimus was achieved in the clinical studies. The proposed target trough concentration range for sirolimus (15 to 25 ng/mL via immunoassay after CsA elimination) for the Rapamune Maintenance Regimen is acceptable. The number of African-Americans were few in these studies. Therefore, trough concentrations should

be obtained in African-Americans on sirolimus and corticosteroids without CsA in future studies to evaluate the adequacy of the recommended trough concentration range for this group of patients.

C. Methods and Specific Findings of Safety Review

In order to complete the safety analysis for Rapamune®, the following information was reviewed: the Applicant's April 6, 2001 Integrated Summary of Safety (ISS) and ISS JMP datasets and the August 8, 2001 Four-month Safety Update and ISS JMP datasets.

D. Adequacy of Safety Testing

Overall the safety testing was adequate except for the following areas. Additional information is needed regarding the use of the cyclosporine-sparing and sirolimus concentration-controlled regimen in Hispanic and Black patients and in patients who receive renal transplants from living-related and living-unrelated donors.

E. Summary of Critical Safety Findings and Limitations of Data

The designs of studies 310 and 212, though similar, were distinct, especially with regard to the time of randomization. Therefore, the data from the 2 studies have not always been integrated. If the safety analyses from the 2 trials are presented together, where possible, the similarities and differences in the results between the 2 studies are defined.

Study 310 is the pivotal study, which was conducted worldwide with a total of 525 renal allograft patients. The supportive study, study 212, was conducted in the United States and Europe with a total of 246 patients. The data for study 310 include complete 12-month data as well as cumulative data beyond 12 months up to the database cutoff date (03 Jan 2001, at which time all patients who were still participating in the study had received at least 15 months of therapy).

Deaths

The following table (Table 6) lists the patients who died in study 310 (from the time of enrollment through the cutoff date of 3 January 2001) and study 212 (final 12 month data).

Table 6 Summary of Deaths in studies 310 and 212

Patient Groups	Study 310	Study 212
RAPA + CsA	12/215 (5.6%)	4/97 (4.1%)
RAPA	8/215 (3.7%)	4 /100 (4.0%)
Non-randomized	17/95 (17.9%)	4 /49 (8.2%)
Total patients	525	246

Medical Officer Comments: *There were no major differences in the number of deaths across the Rapamune®/cyclosporine (RAPA + CsA) and Rapamune® concentration – controlled /cyclosporine withdrawal (RAPA) treatment arms for studies 310 and 212. There were more deaths in the non-randomized patients in both studies which may reflect the selection criteria which aimed to enroll a healthier and more stable patient population that was expected to tolerate cyclosporine withdrawal.*

Causes of death in the RAPA+ CsA treatment arm included the following: 1 interstitial pneumonitis at day 555, 2 cardiac arrests, 1 myocardial infarction, 1 pulmonary edema, 1 sudden death, 3 cases of sepsis, 1 aspergillosis, 1 central nervous system hemorrhage and 1 diabetic complication.

Causes of death in the RAPA arm included 1 death due to aspergillosis, 3 cardiac arrests, 1 cardiac dysfunction and 3 sepsis deaths.

Cause of death in the non-randomized group included 8 cardiac events of which 4 were myocardial infarctions, 6 infections (3 pneumonias, 1 urinary tract infection and 2 sepsis cases), 1 peritoneal bleed, 1 pulmonary embolus and 1 intracranial bleed.

The causes of death were similar across the treatment arms and reflect the complications seen in an immunosuppressed patient population with underlying diseases such as diabetes. None of the deaths were directly attributed to complications from sirolimus therapy.

Discontinuations

Table 7 below outlines the rates of discontinuation in studies 310 and 212.

Table 7 Discontinuations During Treatment through Month 12*

	RAPA + CsA	RAPA	p value**
Study 310	**38/215 (17.7%)**	**58/215 (27%)**	**0.027**
Study 212	**20/97 (20.6%)**	**25/100 (25%)**	**0.499**

*From the FDA January 2002 Advisory Committee Presentation

**Fisher's Exact

Medical Officer Comments: Discontinuations after randomized assignment to treatment is problematic in open-label studies. More patients discontinued during assigned treatment in the cyclosporine withdrawal group(RAPA) compared to the cyclosporine maintenance group(RAPA + CsA). Discontinuations were mainly due to adverse events. However, all patients were followed through 12 months for rejection, graft loss, and death, whether they continued assigned treatment or not. The majority also had retrievable renal function information.

The reasons for discontinuation in pivotal study 310 are listed in Table 8 below.

Table 8* **Reasons for Discontinuation in Pivotal Study 310**

Reason	Rapa + CsA (n=215)	Rapa (n=215)
Total	**38 (18)**	**58 (27)**
Adverse Event	30 (14)	37 (17)
Unsatisfied Response	4 (2)	10 (5)
Patient Request	3 (1)	6 (3)
Protocol Violation	1 (<1)	4 (2)
Other	0	1(<1)

*From the FDA January 2002 Advisory Committee meeting

Medical Officer Comments: ***Although the overall rate of discontinuation in study 310 is significantly higher for the RAPA treatment arm —comparison of the individual reasons for discontinuation failed to show any noteworthy differences.***

There were no predominant causes for discontinuation in either treatment group. The adverse events in study 310 that most frequently led to discontinuation included hypercholesterolemia (RAPA 2.8 % vs. RAPA + CsA 1.4 %), increased creatinine (1.9% in both arms) overdose (3.3% only in the RAPA +CsA arm), infection (RAPA 0.9% and RAPA+ CsA 1.4%), pneumonia (1.4% in both arms)

Table 9* **Study 310 discontinuations reported in the 4 month Safety Update**

Reason for Discontinuation	RAPA CsA N=215	RAPA N=215
Adverse Reaction	**42(20)**	**43(20)**
Failed to return	**1(<1)**	**0**
other	**2(<1)**	**1 (<1)**
Other non-medical event	**1(<1)**	**0**
Patient request	**3(<1)**	**6(3)**
Protocol stipulation	**0**	**0**
Protocol violation	**1 (<1)**	**4(2)**
Unsatisfactory response-efficacy	**9(<4)**	**11(5)**
Total	**59 (27)**	**65(30)**

*From Applicant's 4 month Safety update

Medical Officer Comments: ***In the 4 month Safety Update, study 310 discontinuations were again evaluated. No major difference in the discontinuation rate across treatment arms was noted.***

Table 10 Study 310 Discontinuations due to pneumopathy

	RAPA CSA (n=215)	RAPA (n=215)
Pneumonia- like process	5 (2.3%)	7 (3.2%)
Pneumopathy (no infectious etiology identified)	2/5 (40%)	4/7 (57%)

Medical Officer comments: In post-marketing studies, Rapamune® has been associated with the development of pulmonary infiltrates for which an infectious etiology could not be identified. This process or pneumopathy appears to improve with discontinuation of the drug. In pivotal study 310, there was no major difference across treatment arms regarding the number of patients who discontinued treatment either with a pneumonia-like process or pneumopathy. However, there were two patients who discontinued treatment in the RAPA group whose clinical course was consistent with a pneumopathy due to Rapamune®. For both of these patients, the pulmonary process resolved with discontinuation of Rapamune®. In study 212, there was only one patient who discontinued treatment for a respiratory process and that was a RAPA patient with lung edema.

Patient and graft survival

Patient and graft survival rates were high i.e. well over 90%. Despite the difference in discontinuation from study drug between treatment groups in study 310, patient and graft survival among those in the RAPA arm was not inferior to those in the RAPA + Cyclosporine (CsA) arm.

Table 11* Patient and Graft Survival at 12 months post-transplant

	RAPA + CsA	RAPA	Difference 95% CI**
Study 310	206/215 **(95.8%)**	209/215 **(97.2%)**	-1.4 (-5.3, 2.5)
Study 212	90/97 **92.8%**	95/100 **95.0%**	-2.2% (9.9, 5.5)

* from the FDA Advisory Committee Briefing Package January 2002

** Difference: (Rapa + CsA) – (Rapa) and the 95% Confidence Interval is based on the normal approximation with continuity correction

Medical Officer comments: We are in general agreement with the Applicant's description and report of patient and graft survival at 12 months after transplantation.

Rejection

Table 12 below presents the rates of acute rejection following cyclosporine withdrawal for the two studies.

Table 12* Acute Rejection Following CsA withdrawal

	RAPA + CsA	RAPA	p –value**
Study 310	9/215 **(4.2%)**	21/215 **(9.8%)**	**0.035**
Study 212	6/97 **(6.2%)**	14/100 **(14%)**	0.098

*From the FDA Advisory Committee presentation January 2002
** Fisher's Exact

Medical Officer Comments: ***There was an excess of acute rejection episodes observed in the RAPA arm compared to the RAPA + CsA arm. This was consistent across both studies. The excess in acute rejection, however, was not associated with a detectable decrease in patient or graft survival at 12 months after transplantation as shown by the high patient and graft survival rates. In addition, the "price" of treating this excess of early and mild rejection does not appear to include an increase in the rates of infection or malignancy as a result of using anti-rejection medicine.***

Renal Function

Renal function at 12 months post transplantation was measured by serum creatinine and GFR as calculated by the Nankivell method. Rather than perform an on-therapy analysis, the analyses of renal function presented below attempted to include all patients with a functioning graft at 12 months, including those who discontinued study drug. There was a small amount of missing data, as reflected by the numbers of subjects included in the following tables.

Table 13 below presents mean GFR at 12 months post renal transplant.

Table 13* GFR (mL/min) at 12 months**

	RAPA +CsA	RAPA	p-value
Study 310	56.1 (1.32) n=191	60.8 (1.35) n= 190	<0.001
Study 212	56.5 (2.01) n=89	66.0(2.01) n=89	<0.001

*From the FDA Advisory Committee Presentation January 2002
**For those with a functioning graft at 12 months. Mean (SE) and p-value for ANCOVA adjusting for baseline and center.

Table 14 below presents similar results for serum creatinine at 12 months.

Table 14* Serum creatinine (umol/mL) at 12 months**

	RAPA + CsA	RAPA	p-value
Study 310	160.5 (4.3) n = 198**	147.0 (4.7) n = 198	<0.0001
Study 212	167.3 (9.2) n= 89	136.0 (5.3) n= 89	0.0001

* From the FDA Advisory Committee Presentation January 2002

**For those with a functioning graft at 12 months. Mean (SE) and p-value for ANCOVA adjusting for baseline and center. One pt. who had an outlying value of 960 was excluded.

Medical Officer Comments: ***In both studies 310 and 212, significant increases in GFR are noted for the RAPA treatment arms when compared to the RAPA + CsA arm. Overall, renal function as measured by Nankivell GFR and serum creatinine is better for patients in the RAPA arm.***

Tables 15 and 16 present GFR and serum creatinine results by post-transplant rejection status.

Table 15* GFR (mL/min) at 12 months by rejection status**

Study	Non-rejectors		Rejectors	
	RAPA + CsA	RAPA	RAPA + CsA	RAPA
310	57.0 (1.41) n=169	64.2 (1.43) n =150	48.9 (3.6) n=22	48.0 (2.74) n=40
212	58.2 (2.14) n = 74	70.9 (1.91) n=70	47.9 (5.15) n=15	47.7 (4.05) n=19

* From the FDA Advisory Committee Presentation January 2002
**For those with a functioning graft at 12 months. Mean (SE). Rejection pre-or post randomization.

Table 16 presents similar results for serum creatinine.

Table 16* Serum Creatinine (umol/L) at 12 months by rejection status**

Study	Non-rejectors		Rejectors	
	Rapa + CsA	Rapa	Rapa + CsA	Rapa
310	157 (4.5) n=176	135.7 (4.5) n=157	189.0 (11.3) n= 22***	190.2 (12.7) n=41
212	153.7 (7.0) n=74	123.5 (4.7) n=70	234.5 (38.7) n=15	181.9 (13.2) n=19

* From the FDA Advisory Committee Presentation January 2002
**For those with a functioning graft at 12 months. Mean (SE). Rejection pre- or post-randomization.
***One patient who had outlying value of 960 was excluded.

Medical Officer Comments: ***In tables 15 and 16 above, patients who have not had a rejection within the first 12 months post-transplant show improvement in serum creatinine and GFR in the RAPA arm compared to RAPA + CsA. Patients who experience a rejection, have decreased renal function, regardless of treatment.***

Adverse Events
The data for patients in the randomized groups showed that in both studies, treatment emergent adverse events (TEAEs) were reported in greater than 96% of patients.

In the original Rapamune® NDA which was approved in September 1999, significant differences in adverse events that occurred at a frequency of **greater than 20%** were noted between use of the higher dose of 5 mg Rapamune® vs the lower 2 mg dose. These events included fever, diarrhea, anemia, leukopenia, thrombocytopenia and hyperlipidemia.

Consequently, this safety review focused on ascertaining whether these side effects would be more problematic in the current studies especially in the RAPA group(concentration-controlled sirolimus) with its attendant higher sirolimus exposure.

The findings indicate that diarrhea in study 212, and thrombocytopenia in both study 212 and 310 occurred at a significantly higher incidence in the RAPA groups. The incidence of hypercholesterolemia and hypertriglyceridemia and the use of lipid lowering agents was not significantly different across the two treatment arms in study 212 and 310. Sixty five to 70% of study patients in both treatment arms were on HMG Co-A reductase inhibitors.

In the original Rapamune NDA which was approved in September 1999, significant differences in adverse events that occurred at a frequency of **greater than 5% and less than 20%** were noted between the use of the higher 5 mg Rapamune® dose vs the lower 2 mg Rapamune® dose. These events included chills, face edema, hypotension, hypokalemia, increased LDH, skin ulcer, lymphocoele, tachycardia, insomnia and epistaxis. In the present studies, 310 and 212, the hypokalemia occurred in a significantly greater frequency in the RAPA arm. There were no discontinuations for hypokalemia.

***Medical Officer Comments*: During these trials, no new problems associated with the use of sirolimus emerged.**

The following sections will address specific types of adverse events such as hyperlipidemia, liver function abnormalities, hypokalemia, infection and malignancy, hematologic adverse events and cyclsporine-related toxicities.

Lipids

Table 17* **Study 310 On Treatment Cholesterol analysis**

	RAPA	RAPA + CsA
Randomized Pts. with lipid data	215	214
Randomized Pts. with fasting baseline cholesterol	151/215 (70.2%)	147/214 (69%)

data		
Randomized pts. with baseline, fasting cholesterol less than 200 mg/dl	96/151 (64%)	84/147 (57%)
Randomized pts. with baseline, fasting cholesterol less than 200 mg/dl who developed cholesterol ≥ 240 mg/dl on study drug **	71/96 (74%)	59/84 (70.2%)

* FDA analysis
**developed hypercholesterolemia in segment 3(median time for event was day 91 and mean was day 134)

Table 18* **Study 212 On Treatment Cholesterol analysis**

	RAPA	**RAPA + CsA**
Randomized Pts. with lipid data	100	97
Randomized Pts. with fasting baseline cholesterol data	100	97
Randomized pts. with baseline, fasting cholesterol less than 200 mg/dl	42(42)	43(44.3%)
Randomized pts. with baseline, fasting cholesterol less than 200 mg/dl who developed cholesterol ≥ 240 mg/dl on study drug **	31(74%)	28 (65%)

* FDA analysis
**developed hypercholesterolemia in segment 3(median time for event was day 91 and mean was day 134)

***Medical Officer comments:* Regarding the development of hypercholesterolemia on therapy, there were no major differences noted across treatment arms in both study 310 and 212.**

Table 19* **Study 310 On treatment Triglyceride analysis**

	RAPA	**RAPA + CsA**
Randomized Pts. with lipid data	215	214
Randomized Pts. with fasting baseline TG data	215	214
Randomized pts. with baseline, fasting TG less than 200 mg/dl	115(53.5%)	109(51%)

Randomized pts. with baseline, fasting TG less than 200 mg/dl who developed ≥ 500mg/dl on study drug in segment**	23(20%)	17(16%)

* FDA analysis
**developed hypertriglyceridemia in segment 3(median time for event was day 91 and mean was day 134)

Table 20 * Study 212 On treatment Triglyceride analysis

	RAPA	RAPA + CsA
Randomized Pts. with lipid data	100	97
Randomized Pts. with fasting baseline triglyceride data	63(63%)	68(70%)
Randomized pts. with baseline, fasting TG less than 200 mg/dl	41(65%)	48(71%)
Randomized pts. with baseline, fasting TG less than 200 mg/dl who developed TG ≥ 500 mg/dl on study drug **	8(19.5%)	12(25%)

* FDA analysis
**developed hypertriglyceridemia in segment 3(median time for event was day 91 and mean was day 134)

***Medical Officer Comments*: There is no difference in the development of new onset hypercholesterolemia or hypertriglyceridemia between the two treatment arms in study 310 and 212.**

Liver function
Hepatitis B and hepatitis C antibody data was not available on all patients.

There was an increased incidence of elevated liver function tests (LFTs) in the RAPA vs the RAPA-CsA treatment arms of study 310.

Table 21 Elevated Transaminases in Study 310

	RAPA+ CsA (N=215)	RAPA (N=215)
AST	2.8%	9.8%
ALT	4.2%	13.5%

***Medical Officer comments*: Transaminase values were higher in the RAPA treatment arm for study 310. There were more discontinuation for elevated LFT's in the RAPA treatment arm of study 310 (7 patients) and no discontinuations for elevated LFT's in the RAPA + CSA arm. Mean levels of alkaline phosphates were similar across treatment arms in both study 310 and 212.**

Hypokalemia

Patients were evaluated to determine if there was a difference in the incidence of the development of on- treatment hypokalemia (potassium level less than 3 mmol/L) between the two treatment arms (see Table 22 below).

Table 22 On –treatment Hypokalemia

Study	RAPA	RAPA + CsA
310	**37/215 (17.2%)**	**19/215 (9%)**
212	16/100 (16%)	21/97 (21.7%)

Medical Officer Comments: ***In study 310, there was a higher incidence of hypokalemia in the RAPA treatment arm.***

Infection and malignancy

In general, the rates and types of infection were typical for those seen in the transplant population. There were no significant differences in the rates of infection between the 2 randomized groups in either study (with the exception of higher rates in study 310 of herpes zoster (VZV) infection in the RAPA + CsA group and higher rates in study 212 of fungal dermatitis in the RAPA group).

Medical Officer comments: ***No specific reason emerged to explain the increased incidence of the zoster and fungal dermatitis infections. The study populations were not routinely screened pre-transplant for varicella zoster antibody. Consequently, it is unknown whether there was an imbalance in exposure history for varicella zoster virus across the treatment arms.***

It should also be noted that the majority of study patients in both treatment arms were at lower risk to develop CMV infection (see Tables 2 and 3). In study 310, in the RAPA arm there were 26/215 (12.1 %) high risk patients (CMV negative recipients of CMV positive organs) and in the RAPA + CsA arm there were 30/215(13.9%). There was no imbalance across the treatment arms regarding risk to develop invasive CMV infection.

Table 23 below outlines the use of antibody therapy for treatment of rejection and for prophylaxis in studies 310 and 212.

Table 23 * Antibody use (ATG or OKT3) as prophylaxis and for treatment of acute rejection in studies 310 and 212

	Study 310			Study 212		
	RAPA + CSA	**RAPA**	**Non-random**	**RAPA +CSA**	**RAPA**	**Non-random**
Treatment with antibody and noted as pre-randomization or post-randomization or followup (F/U)	**Pre** 6/215 **(2.8%)** **Post** 0	**Pre** 4/215 **(1.9%)** **Post** 2/215 **(0.9%)**	**Pre** 10/215 **(10.5%)** **Post** 0 **F/U** 5/95 **(5.3%)**	6/97 **(6.2%)**	9/100 **(9.0%)**	3/49 **(6.1%)**
Prophylaxis W/in 48 hours or up to 7 days if ATN/DGF*				15/97 **(15.5%)**	7/100 **(7.0%)**	22 **(44.9%)**
PTLD	2/215 **(0.9%)**	1/215 **(0.46%)**	1/95 **(1.05%)**	0/97 **(0%)**	1/100 **(1%)**	0/49 **(0%)**

* From the Applicant's 4 month safety update.

Medical Officer Comments: ***Across the RAPA and RAPA + CsA treatment arms in studies 310 and 212, there were no major differences in the use of OKT3 and ATG in either the pre- or post- randomization periods. In study 212, more patients received antibody therapy for ATN/DGF in the RAPA + CsA arm, but there was no increased incidence of post-transplant lymphoproliferative disease (PTLD) in this group.***

As reported by the Applicant, there were 4 cases of lymphoma/PTLD/leukemia in study 310 (2 in the RAPA + CsA arm, 1 in the RAPA arm and 1 case in the non-randomized arm). There was 1 case of PTLD in the RAPA arm of study 212. However, this study 212 patient (21208-0806) was diagnosed on study day 402 with a plasma cell infiltrate suggestive of PTLD. The patient's immunosuppressive medication was stopped and the event resolved within 34 days. The diagnosis of PTLD was never confirmed, and the patient remained in and completed the study.

As reported by the Applicant, the overall rate of malignancy was low: 1.6% (12-month) and 5.1% (cumulative data) in studies 212 and 310, respectively.

Leukopenia

In study 310, patients who had baseline WBC counts of greater than or equal to 4.0 (10^9/L) were assessed to see if there were differences across the treatment arms regarding the development of leukopenia. This analysis was not controlled for differences in the use of Bactrim® and ganciclovir. In the RAPA arm 43/215 (20%) patients developed

leukopenia on treatment and in the RAPA + CsA arm there were 46/215 (21.4%) who developed leukopenia.

Medical Officer: Regarding the development of leukopenia, there was no difference across treatment arms in study 310.

Thrombocytopenia
In studies 310 and 212, the **mean** platelet counts were lower in the patients in the RAPA group when compared to the RAPA + CsA group. However, the mean platelet counts for the RAPA group were still in the normal range.

Table 24 presents data looking at specific levels of thrombocytopenia.

Table 24

	RAPA	RAPA + CsA
Study 310		
Platelets < 100,000	42 (19.5%)*	36 (16.7%)*
Platelets < 50,000	3 (1.4%)	5 (2.3%)
Study 212		
Platelets < 100,000	44 (44%)	29 (30%)

* one patient had a baseline less than 100,000 platelets.

Medical Officer Comments: Table 24 demonstrates that there was no major difference across treatment arms in study 310 in regard to thrombocytopenia at a laboratory value of less than 100 (10^9/L) and 50 (10^9/L). However, there was a difference noted in study 212 with more cases of thrombocytopenia (less than 100,000 platelets) occurring in the RAPA arm.

Cyclosporine -associated side effects

Hirsutism and Gingival Hyperplasia
In study 310, the number of patients, who did not have hirsutism pre-study and who developed persistent hirsutism on study, was evaluated. In the RAPA arm, 14/215 (6.5%) patients developed persistent hirsutism and in the RAPA + CsA arm 24/215 (11.2%). In the RAPA arm, 3/215 patients (1.4%) developed persistent gingival hyperplasia and in the RAPA + CsA arm 9/215 patients (4.2%)

Medical Officer comments: In study 310, there was a decrease in cyclosporine side-effects such as persistent hirsutism and gingival hyperplasia in the RAPA treatment arm. There was no difference in the incidence of persistent tremor or headache across the treatment arms in study 310.

Hypertension

In study 310, the systolic and diastolic pressures were significantly lower in the RAPA patients compared to the RAPA + CsA treatment arm.

Summary of findings related to adverse events
The Applicant has made the following observations which are based on the cumulative post-randomization data for study 310 and the 12-month data for study 212:

-Hypertension and edema were reported more frequently in the RAPA + CsA groups in both studies.
-Thrombocytopenia, hypokalemia, and abnormal liver function tests were reported more frequently in the RAPA groups in both studies.
-Treatment emergent adverse events (TEAEs) which were reported more frequently in the RAPA + CsA group included increased creatinine, CsA toxicity (overdose), and hyperuricemia in study 310 and hypervolemia, dyspnea, and hypomagnesemia in study 212.
-TEAEs reported more frequently in the RAPA group included increased alanine aminotransferase (ALT or SGPT) in study 310 and diarrhea and atrial fibrillation in study 212.

Medical Officer Comments: ***We are in agreement with the Applicant regarding the findings related to adverse events seen in studies 310 and 212.***

VIII Dosing Regimen and Administration Issues

Please see the Clinical Pharmacology review for additional information.

Hepatic and Renal Impairment

Medical Officer Comments: ***Information obtained from review of the present supplemental NDAs has not resulted in changes to the hepatic and renal impairment sections of the sirolimus label.***

IX Use in Special Populations

Gender Effects Analyses

Please see the Clinical Pharmacology review for additional information.

Medical Officer Comments: ***Significant differences in gender were not found for trough concentrations.***

Weight

Medical Officer Comments: ***No information has been added to the Rapamune® label regarding weight and sirolimus dosing. Rapamune® is presently given as a fixed dose.***

Race

Medical Officer Comments: As stated in the Clinical Pharmacology review, there were too few Blacks in the studies to perform statistical analyses to determine whether there were significant differences in the sirolimus doses and trough concentrations for this population.

Age/Pediatric and Geriatric Experience

Medical Officer comments: No additional information has been added to the Rapamune® label regarding the use of Rapamune® in the geriatric or pediatric population.

Pregnancy

Medical Officer comments: Rapamune® is Pregnancy Category C and is not indicated for use during pregnancy. Women must use effective contraception during and for 12 weeks after Rapamune® therapy has been stopped. No changes have been made to the pregnancy section of the Rapamune® label as a result of this review.

X. Conclusions and Recommendations

After reviewing the results of clinical studies 310 and 212, it is still not possible to adequately identify the US renal transplant population that can safely use and will most benefit from the cyclosporine-sparing, sirolimus concentration-controlled regimen.

Efficacy
Overall, it appears that the "price" of a cyclosporine-sparing regimen appears to be an increase in early mild-to-moderate acute rejection. However, this increase in rejection rates does not appear to compromise patient and graft survival at 12 months.

Safety
We agree with the Applicant that patients in the cyclosporine-sparing/ sirolimus concentration-controlled arm (RAPA) experienced less toxicity from cyclosporine . However, whether improved renal function will be sustained at 24 months post-transplant still must be determined (see phase 4 commitments below). It was also recommended that studies should be done to more precisely identify the most safe and efficacious dose ranges for sirolimus.

Finally, patients in the cyclosprorine-sparing /sirolimus concentration-controlled arm did experience some additional sirolimus related toxicities such as hypokalemia, thrombocytopenia and elevated LFTs. However, these adverse events appear to be toxicities that the clinician can identify and manage.

Approvability

After completing the review of these applications, the indication for use of Rapamune® in a cyclosporine withdrawal regimen was considered to be "approvable". This action was supported by the January 24, 2002 Advisory Committee member comments regarding the need to determine the optimal sirolimus dose and method of therapeutic drug monitoring (TDM) and to identify the renal transplant population who will most benefit from using this sirolimus concentration-controlled and cyclosporine-sparing regimen.

Before the applications may be approved, the Applicant must present an intent-to-treat analysis of efficacy and safety parameters up to 24 months, and address the heterogeneity of the US renal transplant population. Therefore it will be necessary to:

Conduct an intent-to-treat analysis of safety, acute rejection, patient survival and graft survival, and change in renal function over time up to 24 months post-transplantation in Study 310, which would demonstrate sustained improvement in renal function after withdrawal of cyclosporine. This analysis should include measurement of renal function at 6, 12, 18 and 24 months post transplantation, in all subjects randomized, whether or not they continued on study drug. It is recommended that such analyses include a slope intercept analysis of serum creatinine clearance over time.

Complete post-marketing commitment to provide long-term information from studies 301 and 302, including intent-to-treat information on renal function, and whether or not patients continued on study drug or not. The 24-month reports submitted for these studies have only included on-therapy analyses of renal function, and therefore do not meet the Phase 4 commitment. It will be important to include a slope intercept analysis of serum creatinine clearance.

Collect completed information from ongoing Study 316, evaluating calcineurin inhibitor withdrawal in stable renal transplants. The study report should include intent-to-treat analyses of efficacy and safety parameters, including but not limited to renal function, acute rejection, patient survival, and graft survival. The study report should also include complete follow-up of renal function, noting whether or not patients remained on assigned study therapy. To support a cyclosporine withdrawal indication, this study should demonstrate improved renal function over time after calcineurin inhibitor withdrawal compared to calcineurin inhibitor maintenance in an intent-to-treat analysis.

Complete all post-marketing commitments with respect to high-risk patients, including Black patients.

Define a therapeutic concentration range for sirolimus therapeutic drug monitoring in renal transplant patients whose cyclosporine has been eliminated by providing data and analyses that support this range and identification of the minimal efficacious and maximum tolerated (safe) concentration.

If unable to provide all of the information requested above, it would be necessary to conduct an additional adequate well-controlled trial of cyclosporine withdrawal and concentration-controlled sirolimus in U.S. renal transplant patients. This study should address the heterogeneity of U.S. renal transplant recipients and, keeping in mind that all post-marketing commitments must be fulfilled, it could be used in place of our second request above as long as the results support such an action. This should be at least a one-year study, with a commitment to providing additional long-term follow-up to at least 3 years, designed to evaluate a therapeutic range for concentration-controlled sirolimus. Patients could be randomized to two different sirolimus concentration ranges or to a control. The study randomization should include stratification by ethnicity (e.g., Black patients) and by living-donor versus cadaveric donor, to allow prospectively defined analyses of these sub-populations of interest. This study could be used to validate an assay for quantitating sirolimus in whole blood that would have an acceptable performance characteristic. In addition the study could be used to evaluate low-dose cyclosporine with a fixed, or perhaps higher, dose of sirolimus as an alternative to cyclosporine withdrawal.

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/s/

Matthew Bacho (for Rosemary Tiernan, MD)
5/22/03 03:37:38 PM
CSO

Please type "NDAs 21-083/S-006 & 21-110/S-004" into the signature comments field.

Marc Cavaille Coll
5/22/03 03:42:04 PM
MEDICAL OFFICER
NDAs 21-083/S-006 & 21-110/S-004

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-590	2. NDA NUMBER 21-083
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Wyeth-Ayerst Laboratories P.O. Box 8299 Philadelphia, PA 19101-8299		4. AF NUMBER 5. DOCUMENT(S) NUMBER(S) DATE(S) SE1-006 4/6/01
6. NAME OF DRUG Rapamune	7. NONPROPRIETARY NAME sirolimus	
8. SUPPLEMENT(S) PROVIDES FOR: the elimination of cyclosporine from the immunosuppressive regimen 2 to 4 months after transplantation.		9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES NC 4/25/01
10. PHARMACOLOGICAL CATEGORY Immunosuppressant	11. HOW DISPENSED |X| Rx | | OTC	12. RELATED IND/NDA/DMF(S) N21-110/SE1-004
13. DOSAGE FORM(S) Oral Solution	14. POTENCY(IES) 1 mg/mL	
15. CHEMICAL NAME See current package insert		16. MEMORANDA

17. COMMENTS

Rapamune (sirolimus) Oral Solution was approved on September 15, 1999 for the prophylaxis of organ rejection in patients receiving renal transplants. A 1-mg tablet was approved for this indication on August 25, 2000 (NDA 21-110).

The current supplement provides for the elimination of cyclosporine from the immunosuppressive regimen 2 to 4 months after transplantation. There are no changes to drug substance and drug product CMC associated with this supplement.

A categorical exclusion from the environmental assessment requirements is claimed, in accordance with 21 CFR 25.31(b), for this supplemental application. The Expected Introduction Concentration (EIC) is below 1 part per billion. The applicant knows of no extraordinary circumstances associated with the proposed action. The categorical exclusion is acceptable.

A common package insert is used for the both the oral solution and tablet formulations. The draft package insert submitted with this efficacy supplement includes reference to a 2-mg tablet in the Description and How Supplied sections, in anticipation of approval of N21-110/SCF-003. An Approvable Letter was issued on September 26, 2001 for the aforementioned sNDA. Supplements providing for a revision to the storage statement for the oral solution have been submitted to both NDAs. The labeling associated with this efficacy supplement will need to be harmonized with the labeling changes made in conjunction with other supplements to the Rapamune NDAs.

18. CONCLUSIONS AND RECOMMENDATIONS

This supplemental new drug application is approvable from the chemistry, manufacturing and controls perspective, pending revisions to the package insert.

19. REVIEWER	SIGNATURE	DATE COMPLETED
Mark R. Seggel	{See appended electronic signature page}	September 27, 2001

20. CONCURRENCE: HFD-590/NSchmuff {See appended electronic signature page}

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/s/

Mark Seggel
9/28/01 11:54:20 AM
CHEMIST

Norman Schmuff
10/1/01 06:57:48 AM
CHEMIST

WYETH-AYERST PHARMACEUTICALS

8299, PHILADELPHIA, PA 19101 • (610) 971-5970

Division of American Home Products Corporation

March 15, 2001

Environmental Assessment

Statement of Compliance

Wyeth-Ayerst Pharmaceuticals states that an Environmental Assessment (EA) for the proposed action, the Supplemental New Drug Application for the cyclosporine elimination indication for Rapamune® (sirolimus), is categorically excluded according to 21 CFR 25.31(b).

The aforementioned regulation states that a categorical exclusion is permitted for "Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion." The Expected Introduction Concentration (EIC) of Rapamune® (sirolimus), is below 1 part per billion.

To the best knowledge of Wyeth-Ayerst Pharmaceuticals, no extraordinary circumstances exist associated with the proposed action.

Craig F. Seyfried
Senior Director
Environmental Health & Safety
Wyeth-Ayerst Pharmaceuticals

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDAs:	21-083/SE1-006
	21-110/SE1-004
Name of drug:	Rapamune (sirolimus) Oral Solution
	Rapamune (sirolimus) Tablets, 1 mg
Applicant:	Wyeth-Ayerst Research
Indication:	Elimination of cyclosporine from the immunosuppression regimen 2-4 months post transplantation
Documents reviewed:	_____
	_____
	_____
Project manager:	Matthew Bacho
Clinical reviewer:	Marc Cavaillé-Coll, M.D. - efficacy
	Rosemary Tiernan, M.D. - safety
Dates:	Received 4/9/01; user fee 2/9/02; AC meeting 1/24/02
	Received 4/18/01; user fee 2/18/02; AC meeting 1/24/02
Statistical reviewer:	Cheryl Dixon, Ph.D.
Statistics team leader:	Karen Higgins, Sc.D.
Biometrics division director:	Mohammad Huque, Ph.D.

Keywords: NDA review, clinical studies, immunosuppression,

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The initial approval of Rapamune was obtained in September 1999 for the oral solution formulation. This approval was based on two phase III studies in which Rapamune was shown to effectively prevent acute rejection in patients receiving renal transplants when used in combination with cyclosporine (CsA) and corticosteroids. In August 2000, the tablet dose form was approved. A clinical study comparing the 2-mg tablet to 2-mg oral solution was submitted to support this approval since the two dosage forms are not bioequivalent.

Even though treatment with Rapamune was associated with a significant reduction in the rate of acute rejection at 6 months and equivalent patient and graft survival at 12 months, renal function at 12 months was decreased. The immunosuppressive effects of Rapamune and CsA are synergistic and it has been suggested that Rapamune therapy may exacerbate CsA nephrotoxicity. Therefore, a regimen that minimized long-term exposure to CsA was considered. This application presents data from two studies to support a CsA sparing indication. For this indication, it is recommended that Rapamune be used initially in combination with CsA and corticosteroids and then consider CsA elimination 2 to 4 months after transplant.

The studies reviewed consisted of a pivotal study and a supportive study. The pivotal study, Study 310, was an open label, randomized, non-IND, phase III study conducted in Europe, Canada, and Australia. The supportive study, Study 212, was an open-label, randomized, phase II study conducted under the US IND in Europe and the United States. In these studies, patients were randomized to one of 2 treatment groups: fixed dose Rapamune (2 mg/day) with CsA or concentration controlled Rapamune with CsA elimination 3 months following transplantation. Both studies were designed to address patient and graft survival, acute rejection, and renal function at 12 months though the endpoint considered primary was different between the 2 studies.

1.2 PRINCIPAL FINDINGS, CONCLUSIONS, AND RECOMMENDATIONS

The two studies submitted to provide evidence for a Rapamune treatment regimen with a withdrawal of CsA 2 to 4 months post randomization are supportive of one another. The results indicate that patient and graft survival 12 months post transplantation is high and equivalent between treatment regimens. In addition to the high graft survival rates at 12 months, renal function at 12 months was significantly better for the patients who had CsA withdrawn and continued to receive Rapamune only compared to those who received Rapamune with CsA. However, there is an increase in acute rejections following CsA withdrawal. It cannot be determined from the data collected the type of patient who may be at higher risk for a rejection episode following CsA withdrawal and whether this is a clinically important event in terms of long-term

graft survival. The data does indicate that renal function at 12 months for a patient who experiences an acute rejection during the first 12 months post-transplantation is reduced compared to those who do not experience an acute rejection. This reduction in renal function for patients who experience an acute rejection is evident regardless of treatment group. It is difficult to determine whether the short term improvement in renal function with CsA withdrawal, considering the increased incidence of an acute rejection following the withdrawal of CsA, will lead to long term graft survival without longer term follow-up data.

In addition, it is difficult to determine the patient population who may benefit from CsA withdrawal. The population studied is not entirely consistent with the current US kidney transplantation population. There were few blacks and other non-white populations studied and few living donor transplants studied. It is possibly easier to say who should not be considered for CsA withdrawal rather than say who should be considered for CsA withdrawal based on the current data.

Therefore, it is recommended that longer-term renal function and graft survival data be collected to determine the clinical impact of improved renal function on long-term graft survival. It is also recommended that patients more applicable to the US kidney transplant population be studied.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

The initial approval of Rapamune was obtained in September 1999 for the oral solution formulation. This approval was based on two phase III studies in which Rapamune was shown to effectively prevent acute rejection in patients receiving renal transplants when used in combination with cyclosporine (CsA) and corticosteroids. In August 2000, the tablet dose form was approved. A clinical study comparing the 2-mg tablet to 2-mg oral solution was submitted to support this approval since the two dosage forms are not bioequivalent.

Even though treatment with Rapamune was associated with a significant reduction in the rate of acute rejection at 6 months and equivalent patient and graft survival at 12 months, renal function at 12 months was decreased. The immunosuppressive effects of Rapamune and CsA are synergistic and it has been suggested that Rapamune therapy may exacerbate CsA nephrotoxicity. Therefore, a regimen that minimized long-term exposure to CsA was considered. This application presents data from studies to support a CsA sparing indication. For this indication, it is recommended that Rapamune be used initially in combination with CsA and corticosteroids and then consider CsA elimination 2 to 4 months after transplant.

2.2 DATA ANALYZED AND SOURCES

The data analyzed in this review comes from two studies, a pivotal study and a supportive study. The pivotal study, Study 310, was an open label, randomized, non-IND, phase III study conducted in Europe, Canada, and Australia. The supportive study, Study 212, was an open-label, randomized, phase II study conducted under the US IND in Europe and the United States. The Applicant provided the data from these studies in the electronic submission. In addition to these datasets, the reviewer requested two analysis datasets, one containing data regarding graft loss, acute rejection, and death and one containing lab data for serum creatinine and GFR, for each study from the Applicant. For a complete description of the datasets requested, see the fax dated 12/21/01. These datasets were submitted to the electronic submission on 01/11/02.

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

The following is a brief summary of the Applicant's primary results.

The results of the supportive CsA elimination study were consistent with the pivotal CsA elimination study 310 and they showed the following:

The 12-month acute rejection rates in the CsA elimination arms were 22%. Acute rejection rates in the CsA elimination arms were slightly (but not significantly) higher than those in the groups that received standard dose CsA. There were no differences in the severity of the rejection episodes between the 2 groups.

Renal function at 6 and 12 months was significantly better in patients in the CsA elimination arms.

Patient and graft survival were excellent and comparable in both groups.

2.3.2 STATISTICAL METHODOLOGIES

The statistical methodologies used in this review are:

For binary endpoints, incidence rates, the difference in incidence rates, and confidence intervals about the difference were calculated. The confidence intervals were calculated using the normal approximation to the binomial and the Mantel-Haenszel stratified approach. In some situations, Fisher's exact test was performed.

For continuous endpoints, analysis of covariance (ANCOVA) was used.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.3.3.1 Study 310

Study 310 was designed primarily to assess the equivalence in the rates of graft survival at 12 months after transplantation in recipients of primary or secondary renal allografts who were receiving either continuous therapy with CsA and Rapamune or were receiving a regimen of CsA and Rapamune followed by concentration-controlled sirolimus and CsA elimination. Secondary objectives included the incidence of acute

rejection at 6 and 12 months following transplantation, patient and graft survival 24 and 36 months after transplantation, and renal function at 6, 12, 24, and 36 months. The current submission presents the 12-month results of this 3-year study.

This was an non-IND, phase III, randomized, open label, 2-part study conducted at 57 centers in Europe, Canada, and Australia. A total of 525 patients were enrolled in Study 310. During the first 3 months of the study, when all patients received Rapamune , CsA, and corticosteroids, 95 patients discontinued before random assignment. Three months following transplantation, the remaining 430 patients were randomly assigned 1:1 to either the Rapamune + CsA group or the Rapamune only group. At the time of randomization, patients were stratified by donor source (living versus cadaver). Patients were excluded from randomization if they fulfilled any of the following criteria: Banff grade III acute rejection episode or vascular rejection in the 4 weeks before random assignment, dialysis dependency, serum creatinine > 400 mol/L, or inadequate renal function (in the opinion of the investigator) to support CsA elimination.

Patients in the Rapamune + CsA group received Rapamune (2 mg/day) along with CsA. Patients in the Rapamune only group had their daily dose of Rapamune adjusted to maintain sirolimus trough concentration of 20 to 30 ng/mL until 12 months and then 15 to 25 ng/mL thereafter; the CsA dose was gradually eliminated over the course of 4 to 6 weeks beginning at the 3-month randomization point. Only the tablet formulation of Rapamune was used in this study. Patients in both groups continued to receive corticosteroids.

The primary endpoint for this study was graft survival at 1 year. For the purpose of determining sample size, the rate of graft survival was estimated to be 95% in both groups. Two hundred four patients per group were needed in order to have 90% power to correctly reject the null hypothesis that the difference in the rate of graft survival between the two groups is greater than 7%. A total of 470 patients were to be enrolled to allow for dropouts before randomization.

The primary analysis of graft survival consisted of calculating a two-sided 95% confidence interval around the difference in rates for the two treatment groups. As stated in the protocol, equivalence will be demonstrated if the 95% confidence interval crosses zero and remains within a delta of 7%. All randomly assigned patients were included in this analysis. It should be noted that the Division typically uses a delta of 5% when assessing the non-inferiority of patient and graft survival.

Secondary endpoints defined as binary endpoints were summarized by incidence rates. The difference between the percentages was computed with 95% confidence intervals and the difference between the 2 groups was analyzed by Fisher's exact test. Renal function measures of serum creatinine and GFR were analyzed by analysis of covariance with treatment group as a factor in the model and the baseline measurement as a covariate. For this study, the baseline measurement was the last measurement prior to randomization.

Patient Demographics

A total of 525 patients were enrolled in the study. During the first 3 months, 95 patients discontinued before random assignment. These patients will be referred to as the nonrandomized group and will only be described in this section. At three months, 215 patients were randomized to the Rapamune + CsA group and 215 patients were randomized to the Rapamune only group.

Table 310-1 lists the primary reasons for discontinuation of Rapamune during the first 12 months by treatment group. The primary reasons for discontinuation in the nonrandomized group were adverse event and unsatisfactory response. Discontinuation after random assignment to treatment is problematic in open-label studies. It is difficult to determine if the actual regimen led to the discontinuation or if it was due to patient or physician concern over randomized treatment. Among the 430 randomized patients, significantly more patients discontinued treatment in the Rapamune only group than in the Rapamune + CsA group (Fisher's exact p= 0.027). Adverse event was the primary reason for discontinuation of treatment in both treatment groups. All patients were followed for acute rejection, graft loss, and death through 12 months even if they discontinued treatment.

Table 310-1
Reason for Discontinuation of Treatment

Reason, n (%)	Nonrandomized (n=95)	Rapamune + CsA (n=215)	Rapamune (n=215)
Total	95 (100)	38 (17.7)	58 (27.0)
Adverse event	70 (73.6)	30 (14.0)	37 (17.2)
Unsatisfactory response – efficacy	12 (12.6)	4 (1.9)	10 (4.7)
Patient request	4 (4.2)	3 (1.4)	6 (2.8)
Protocol violation	4 (4.2)	1 (<1)	4 (1.9)
Other	5 (5.3)	0	1 (<1)

Table 310-2 summarizes the demographic and baseline characteristics for all enrolled patients. There were no statistically significant differences between the two randomized treatment groups. The majority of the patients were male and white. The transplants were mainly primary transplants and the source of the donor allograft was primarily cadaveric.

Table 310-2
Demographic and Baseline Characteristics

	Nonrandomized (n=95)	Rapamune + CsA (n=215)	Rapamune (n=215)
Gender, n (%)			
Female	35 (36.8)	72 (33.5)	82 (38.1)
Male	60 (63.2)	143 (66.5)	133 (61.9)
Race			
White	90 (94.7)	201 (93.5)	205 (95.4)
Black	1 (1.1)	5 (2.3)	2 (0.9)
Oriental (Asian)	3 (3.2)	4 (1.9)	3 (1.4)
Other	1 (1.1)	5 (2.3)	5 (2.3)
Age mean (SD)	48.8 (13.5)	45.8 (11.6)	44.6 (13.1)
min, max	21, 72	16, 68	16, 73
Transplant			
Primary	83 (87.4)	197 (91.6)	193 (90.2)
Secondary	12 (12.6)	18 (8.4)	21 (9.8)
Primary Etiology			
Autoimmune Disease	3 (3.2)	2 (0.9)	5 (2.3)
Diabetes Mellitus	11 (11.6)	14 (6.5)	17 (7.9)
Failure of Previous Graft	3 (3.2)	2 (0.9)	3 (1.4)
Glomerulonephritis	30 (31.6)	49 (22.8)	44 (20.5)
Hypertension	6 (6.3)	15 (7.0)	11 (5.1)
IgA Nephropathy (Berger's)	9 (9.5)	25 (11.6)	29 (13.5)
Interstitial Nephritis/Pyelonephritis	7 (7.4)	16 (7.4)	19 (8.8)
Obstructive Uropathy/.Reflux	7 (7.4)	8 (3.7)	8 (3.7)
Other/Unknown	7 (7.4)	53 (24.7)	59 (27.4)
Polycystic Disease-Kidney	12 (12.6)	31 (14.4)	20 (9.3)
Donor Source			
Cadaver	89 (93.7)	189 (87.9)	190 (88.4)
Living Related	4 (4.2)	19 (8.8)	18 (8.4)
Living Unrelated	2 (2.1)	7 (3.3)	7 (3.3)
Study Site			
Europe	71 (74.7)	179 (83.3)	176 (81.9)
Canada	8 (8.4)	15 (7.0)	15 (7.0)
Australia	16 (16.8)	21 (9.8)	24 (11.2)

Efficacy Results

The remainder of this review will focus on the 430 patients who were randomized to one of the two treatments.

The results of 12-month graft survival are presented in Table 310-3. Graft loss is defined as physical loss (nephrectomy), functional loss (necessitating maintenance dialysis for more than 8 weeks), retransplant, death, or patients who were lost to follow-up. All patients, including those who discontinued randomized treatment, had 12-month follow-up with respect to graft loss, death, and acute rejection. The rates of graft survival at 12 months were 95.8% for patients who received Rapamune + CsA and 97.2% for patients who received Rapamune only. These rates were equivalent since the lower bound of the 95% confidence interval about the difference (Rapamune only- Rapamune

+CsA) excluded the protocol-specified delta of 7%. The lower bound also excluded the 5% delta typically used by the Division.

Table 310-3
Graft Survival at 12 Months

	Rapamune + CsA (n=215)	Rapamune (n=215)	Difference 95% CI 95% Stratified CI*
Overall rate of graft survival	206 (95.8)	209 (97.2)	1.4 (-2.5, 5.3) (-2.7, 5.5)
Reason for graft failure			
Pure graft loss	5	2	
Death with a functioning graft	4	4	

*Difference is Rapamune – (Rapamune +CsA)
95% CI is calculated using the normal approximation to the binomial with continuity correction.
95% Stratified CI is calculated using the Mantel Haenszel method weighting by donor source.

Table 310-4 summarizes the incidence of first biopsy-confirmed acute rejection through 12 months. The rates are listed by study period, pre-randomization and post-randomization including follow-up, and total at 12 months. The two treatment groups had similar rates of rejection prior to randomization. During the post-randomization period, there was a statistically significantly higher incidence of rejection in the Rapamune only group (9.8%) compared to the Rapamune + CsA group (4.2%). The excess in acute rejection, however, was not associated with a detectable decrease in patient or graft survival at 12 months after transplantation as shown in Table 310-3 by the high graft survival rates. At 12 months, the overall rates of acute rejection are not statistically different between the two groups. The upper bound of the 95% confidence interval about the difference in rejection rates, however, is greater than what would be considered an acceptable level for non-inferiority.

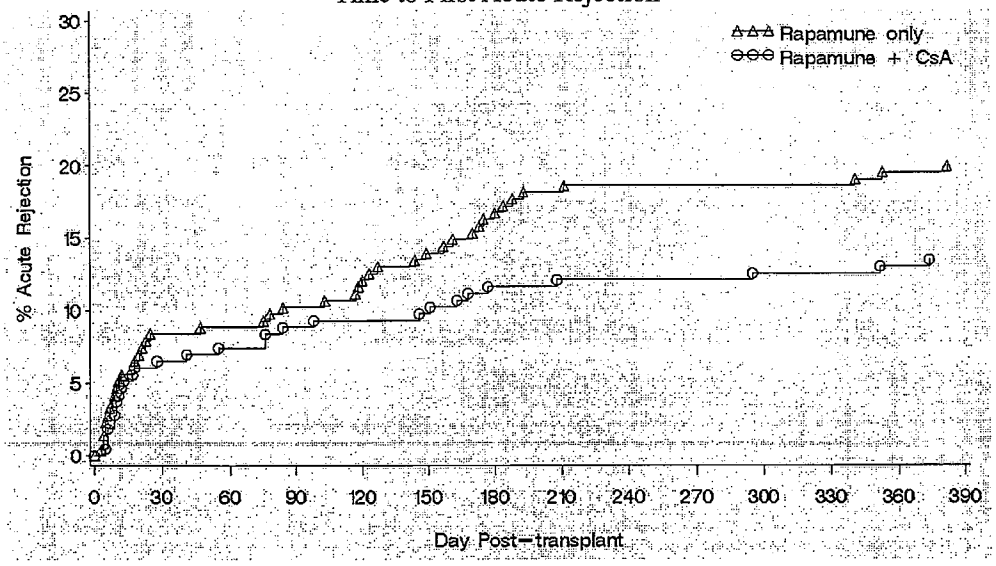
Table 310-4
Acute Rejection through 12 Months

	Rapamune + CsA (n=215)	Rapamune (n=215)	p-value*	Difference, 95% CI
Pre-randomization	20 (9.3)	22 (10.2)	0.871	0.9 (-5.2, 7.0)
Post-randomization**	9 (4.2)	21 (9.8)	0.036	5.6 (0.3, 10.9)
Total	29 (13.5)	43 (20.0)	0.093	6.5 (-1.0, 14.0)

*Fisher's Exact Test
** Including follow-up

Figure 310-1 shows the time to first acute rejection for both the Rapamune + CsA and Rapamune only groups.

Figure 310-1
Time to First Acute Rejection



The incidences of efficacy failure and treatment failure at 12 months are summarized in Table 310-5. Efficacy failure is defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death. Treatment failure is defined as the first occurrence of discontinuation, biopsy-confirmed acute rejection, graft loss, or death. There was no significant difference between treatment groups for efficacy failure. However, the upper bound of the 95% confidence interval about the difference in efficacy failure rates is greater than what would be considered an acceptable level for non-inferiority. There was a significant difference between the two treatment groups in the incidence of treatment failure. This was due to a higher rate of discontinuation and rejection in the Rapamune only group.

Table 310-5
Efficacy Failure and Treatment Failure at 12 Months

	Rapamune + CsA (n=215)	**Rapamune (n=215)**	**p-value***	**Difference, 95% CI**
Overall efficacy failure	34 (15.8)	48 (22.3)	0.110	6.5 (-1.4, 14.4)
Acute Rejection	29	43		
Graft Loss	2	1		
Death	3	4		
Overall treatment failure	55 (25.6)	80 (37.2)	0.013	11.6 (2.4, 20.8)
Discontinuation	28	37		
Acute Rejection	26	43		
Graft Loss	0	0		
Death	1	0		

*Fisher's Exact Test

Safety Results

This review will focus on the evaluation of laboratory parameters regarding renal function. For a complete review of the safety data, please refer to the medical officer safety review written by Dr. Rosemary Tiernan.

Serum creatinine and calculated GFR assess renal function. As a note, lower serum creatinine values and higher GFR values indicate better renal function. The Applicant presented analyses based on those still on therapy at 12 months and using a last observation carried forward for patients who discontinued therapy before completing the 12 month treatment period. An analysis that includes only patients still on therapy may eliminate a significant proportion of patients who had poor renal function. Even though the Applicant states that the results of the two analyses draw similar conclusions, the Division performed an analysis using 12 month data for all patients with a functioning graft (excluding those who had a graft loss or died) whether or not they had discontinued study drug. Since there were a similar number of patients with a non-functioning graft at 12 months in each treatment group, this analysis is reasonable and clinically more relevant. Twelve-month data for those who discontinued was not initially submitted to the sNDA. Therefore, this data had to be requested from the Applicant. The Applicant made an excellent attempt at retrieving this information for the Division given the extenuating circumstances behind the request. However, 5-10% of the patients still had missing 12-month data and was excluded from the following analyses.

Table 310-6 summarizes the results of mean serum creatinine and GFR for patients with a functioning graft at 12 months. Renal function at 12 months is significantly better for patients on Rapamune only compared to those on Rapamune + CsA.

Table 310-6
Mean (SE) Serum Creatinine and GFR at 12 Months

	Rapamune + CsA	Rapamune	ANCOVA p-value*
Serum Creatinine (mol/mL)	160.5 (4.3) n=198**	147.0 (4.7) n=198	<0.0001
GFR (mL/min)	56.1 (1.32) n=191	60.8 (1.35) n=190	<0.0001

* Last measurement before randomization (baseline) and center are covariates.
** One patient who had an outlying value of 960 was excluded from this analysis.

Due to the increased number of acute rejections in the Rapamune only group, it was of interest to consider renal function by whether or not a patient had a rejection in the first 12 months following transplantation. These results are presented in Table 310-7. As seen in this table, renal function is worse for patients who experienced an acute rejection episode regardless of which treatment they were assigned.

Table 310-7
Mean (SE) Serum Creatinine and GFR at 12 Months
By Rejection Status

	No Rejection		Rejection	
	Rapamune + CsA	**Rapamune**	**Rapamune + CsA**	**Rapamune**
Serum Creatinine (mol/mL)	157.0 (4.5) n=176	135.7 (4.5) n=157	189.0 (11.3) n=22*	190.2 (12.7) n=41
GFR (mL/min)	57.0 (1.41) n=169	64.2 (1.43) n=150	48.9 (3.6) n=22	48.0 (2.72) n=40

*One patient who had an outlying value of 960 was excluded from this analysis.

2.3.3.2 Study 212

Study 212 was designed primarily to evaluate, at 6 months, the effect on renal function of concentration controlled Rapamune administered concomitantly with corticosteroids and short-term CsA. Secondary objectives included the incidence of acute rejection, patient and graft survival, and renal function beyond 6 months. The focus of the current submission will be the 12-month results.

This was an open label, randomized, pilot study conducted at 17 centers in the United States and Europe. A total of 246 patients were enrolled in study 212. Within 2 to 7 days after transplantation, patients with good renal function were equally randomized to one of two treatment groups: 1) standard therapy with fixed dose Rapamune and CsA, and 2) concentration controlled sirolimus and reduced dose CsA followed by CsA elimination. Patients with acute tubular necrosis/ delayed graft function were eligible for randomization up to the seventh day after transplantation. The nonrandomized group consisted of 49 patients. Of the remaining patients, 97 were randomized to the Rapamune + CsA group and 100 to the Rapamune concentration controlled group.

Patients in the Rapamune + CsA group received Rapamune (2 mg/day) along with CsA. Patients in the Rapamune only group had their daily dose of Rapamune adjusted to maintain sirolimus trough concentration of 10 to 20 ng/mL until 12 months; the CsA dose was gradually eliminated during month 3. From the start of the study, the targeted concentration ranges of CsA were lower for patients in the Rapamune only group than the Rapamune + CsA group. Only the oral solution formulation of Rapamune was used in this study. Patients in both groups continued to receive corticosteroids.

The primary endpoint for this study was the serum creatinine level of patients. Calculated GFR was a supportive measurement. A sample size of 65 in each group would have 90% power to detect a difference in means as small as 0.4 mg/dL (35.4 mol/L) assuming a common standard deviation of 0.68 using a 2-group t-test with a 0.05 two-sided significance level.

The primary analysis of renal function was based on ANCOVA with treatment group as a factor and the baseline measurement as a covariate. For this study, the baseline measurement was the last measurement prior to CsA withdrawal or the month 2 value for those who were not randomized to have CsA withdrawn. Secondary endpoints of acute rejection and graft and patient survival were summarized by incidence rates. The difference between the percentages was computed with 95% confidence intervals and the difference between the 2 groups was analyzed by Fisher's exact test.

Patient Demographics

A total of 246 patients were enrolled in the study. Forty-nine patients were not randomized. These patients will be referred to as the nonrandomized group and will only be described in this section. Ninety-seven patients were randomized to the Rapamune + CsA group and 100 patients were randomized to the Rapamune only group.

Table 212-1 lists the primary reasons for discontinuation of Rapamune during the first 12 months by treatment group. The primary reason for discontinuation of treatment in all of the groups was adverse event. There was not a statistically significant difference in the rates of discontinuation for the two randomized groups (Fisher's exact p=0.499). All patients were followed for acute rejection, graft loss, and death through 12 months even if they discontinued treatment.

Table 212-1
Reason for Discontinuation of Treatment

Reason, n (%)	**Nonrandomized** (n=49)	**Rapamune + CsA** (n=97)	**Rapamune** (n=100)
Total	28 (57.1)	20 (20.6)	25 (25.0)
Adverse event	19 (38.8)	12 (12.4)	11 (11.0)
Unsatisfactory response – efficacy	3 (6.1)	5 (5.2)	4 (4.0)
Patient request	1 (2.0)	2 (2.1)	6 (6.0)
Protocol violation	1 (2.0)	0	1 (1.0)
Other	4 (8.2)	1 (1.0)	3 (3.0)

Table 212-2 summarizes the demographic and baseline characteristics for all enrolled patients. There were no statistically significant differences between the two randomized treatment groups. The majority of the patients were male and white. All transplants were primary allografts from cadaver donors.

Table 212-2
Demographic and Baseline Characteristics

	Nonrandomized (n=49)	Rapamune + CsA (n=97)	Rapamune (n=100)
Gender, n (%)			
Female	19 (38.8)	42 (43.3)	42 (42.0)
Male	30 (61.2)	55 (56.7)	58 (58.0)
Race			
White	31 (63.3)	71 (73.2)	80 (80.0)
Black	14 (28.6)	18 (18.6)	15 (15.0)
Oriental (Asian)	1 (2.0)	4 (4.1)	2 (2.0)
Other	3 (6.1)	4 (4.1)	3 (3.0)
Age mean (SD)	47.8 (12.8)	44.9 (12.9)	45.2 (11.7)
min, max	19, 75	16, 69	20, 71
Primary Etiology			
Autoimmune Disease	2 (4.1)	2 (2.1)	2 (2.0)
Diabetes Mellitus	13 (26.5)	9 (9.3)	8(8.0)
Glomerulonephritis	13 (26.5)	19 (19.6)	30 (30.0)
Hypertension	11 (22.4)	19 (19.6)	16 (16.0)
IgA Nephropathy (Berger's)	1 (2.0)	9 (9.3)	8 (8.0)
Interstitial Nephritis/Pyelonephritis	2 (4.1)	5 (5.2)	3 (3.0)
Obstructive Uropathy/.Reflux	3 (6.1)	6 (6.2)	9 (9.0)
Other/Unknown	0	14 (14.4)	8 (8.0)
Polycystic Disease-Kidney	4 (8.2)	14 (14.4)	16 (16.0)
Study Site			
United States	37 (75.5)	51 (52.6)	54 (54.0)
Europe	12 (24.5)	46 (47.4)	46 (46.0)

Efficacy Results

The remainder of this review will focus on the 197 patients who were randomized to one of the two treatments.

The results of 12-month graft survival are presented in Table 212-3. Graft loss is defined as physical loss (nephrectomy), functional loss (necessitating maintenance dialysis for more than 8 weeks), or death with a functioning graft. The rates of graft survival at 12 months were 92.8% for patients who received Rapamune + CsA and 95.0% for patients who received Rapamune only. These rates are not statistically different and are very close to the acceptable limit for non-inferiority, -5%.

Table 212-3
Graft Survival at 12 Months

	Rapamune + CsA (n=97)	Rapamune (n=100)	p-value*	Difference, 95% CI
Overall rate of graft survival	90 (92.8)	95 (95.0)	0.564	2.2 (-5.5, 9.9)
Reason for graft failure				
Pure graft loss	4	1		
Death with a functioning graft	3	4		

*Fisher's Exact test. Difference is Rapamune – (Rapamune +CsA). 95% CI is calculated using the normal approximation to the binomial with continuity correction.

Table 212-4 summarizes the incidence of first biopsy-confirmed acute rejection through 12 months. The rates are listed by pre- CsA withdrawal (through month 2), post-CsA withdrawal (months 2 to 12), and total at 12 months. The two treatment groups had similar rates of rejection during the first 2 months. Following CsA withdrawal, there was an increase in the incidence of rejection in the Rapamune only group (14.0%) compared to the Rapamune + CsA group (6.2%). This increase was not statistically significant. However, the upper bound of the 95% confidence interval about the difference in rejection rates is greater than what would be considered an acceptable level for non-inferiority. The excess in acute rejection was not associated with a detectable decrease in patient or graft survival at 12 months after transplantation as shown in Table 212-3 by the high graft survival rates. At 12 months, the overall rates of acute rejection are not statistically different between the two groups. But again, the upper bound of the 95% confidence interval about the difference in rejection rates is greater than what would be considered an acceptable level for non-inferiority.

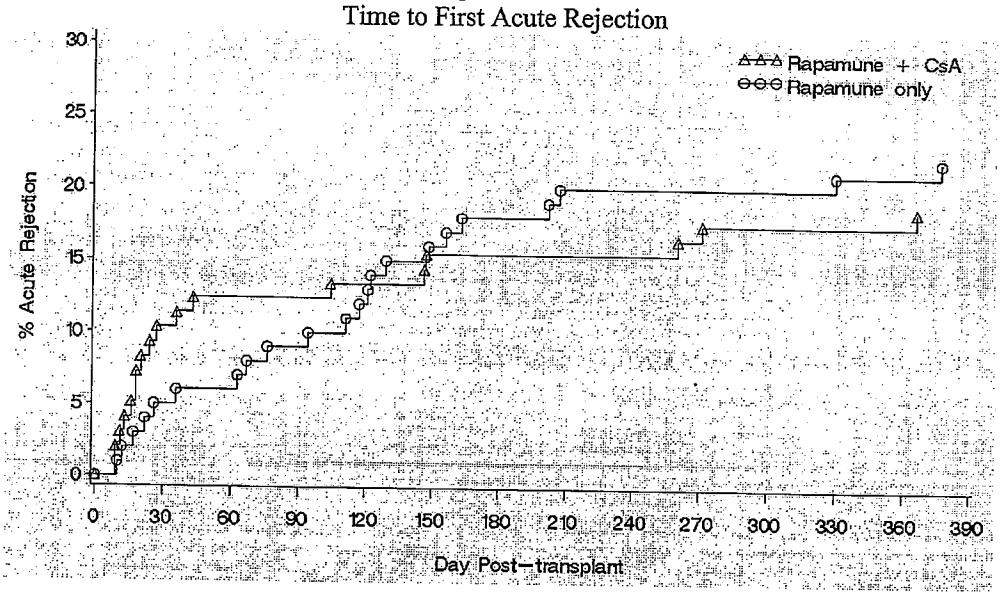
Table 212-4
Acute Rejection through 12 Months

	Rapamune + CsA (n=97)	Rapamune (n=100)	p-value*	Difference, 95% CI
Pre-CsA withdrawal	12 (12.4)	8 (8.0)	0.352	-4.4 (-13.8, 5.1)
Post-CsA withdrawal	6 (6.2)	14 (14.0)	0.098	7.8 (-1.5, 17.1)
Total	18 (18.6)	22 (22.0)	0.598	3.4 (-8.8, 15.6)

*Fisher's Exact Test

Figure 212-1 shows the time to first acute rejection for both the Rapamune + CsA and Rapamune only groups.

Figure 212-1
Time to First Acute Rejection



Safety Results

This review will focus on the evaluation of laboratory parameters regarding renal function. For a complete review of the safety data, please refer to the medical officer safety review written by Dr. Rosemary Tiernan.

Serum creatinine and calculated GFR assess renal function. As a note, lower serum creatinine values and higher GFR values indicate better renal function. An analysis using 12 month data for all patients with a functioning graft (excluding those who had a graft loss or died) whether or not they had discontinued study drug was performed. Six patients in the Rapamune only group and 1 patient in the Rapamune +CsA group had missing 12-month data and were excluded from the following analyses.

Table 212-5 summarizes the results of mean serum creatinine and GFR for patients with a functioning graft at 12 months. Renal function at 12 months is significantly better for patients on Rapamune only compared to those on Rapamune + CsA.

Table 212-5
Mean (SE) Serum Creatinine and GFR at 12 Months

	Rapamune + CsA (n=89)	**Rapamune** (n=89)	**ANCOVA p-value***
Serum Creatinine (mol/mL)	167.3 (9.2)	136.0 (5.3)	0.0001
GFR (mL/min)	56.5 (2.01)	66.0 (2.01)	<0.0001

* Last measurement before CsA withdrawal (baseline) and center are covariates.

Due to the increased number of acute rejections in the Rapamune only group, it was of interest to consider renal function by whether or not a patient had a rejection in the first 12 months following transplantation. These results are presented in Table 212-6. As seen in this table, renal function is worse for patients who experienced an acute rejection episode regardless of which treatment they were assigned.

Table 212-6
Mean (SE) Serum Creatinine and GFR at 12 Months
By Rejection Status

	No Rejection		Rejection	
	Rapamune + CsA n=74	**Rapamune** n=70	**Rapamune + CsA** n=15	**Rapamune** n=19
Serum Creatinine (mol/mL)	153.7(7.0)	123.5 (4.7)	234.5 (38.7)	181.9 (13.2)
GFR (mL/min)	58.2 (2.14)	70.9 (1.91)	47.9 (5.15)	47.7 (4.05)

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

As shown in Tables 310-2 and 212-2, the population studied was primarily white. In the Study 310, the primary study, there were only 8 black patients enrolled. One discontinued prior to randomization, 5 were randomized to the Rapamune + CsA group, and 2 were randomized to the Rapamune only group. These numbers are too small to perform any meaningful subgroup analyses by race. The lack of non-white patients is a concern as to how applicable the population studied is to the United States population where 35% of the patients on the current UNOS waiting list for kidney transplants are black.

Due to the high rates of graft survival, similar rates of graft survival were seen for males and females and for patients 50 years old and >50 years old as were seen for the overall population. In Study 310, patients 50 years old in the Rapamune only group experienced a higher rate of acute rejection at 12 months than those in the Rapamune + CsA group (22.1% vs. 12.5%, Fisher's exact-p=0.0394). There was no difference in the rate of acute rejection for patients > 50 years old nor by gender. Renal function, as assessed by serum creatinine, for these subgroups is not different from the overall population.

2.5 STATISTICAL AND TECHNICAL ISSUES

The primary issue associated with this submission is the applicability of the results seen from these studies to the US population waiting for kidney transplants and the ability to state which patients should be considered for CsA withdrawal and concentration controlled Rapamune. The population studied was primarily white Europeans receiving a cadaveric allograft. The US population awaiting a kidney transplant is more

heterogeneous than the European population, is more than one third black, and is receiving more living allografts.

Another issue is related to a surrogate endpoint situation. It is being assumed that an improvement in renal function over existing therapies at 12 months will correspond to a long-term benefit with respect to graft survival. However, based on the data at hand, this has not been shown. There is an improvement in renal function but without long term follow up data we cannot be sure if this will continue and lead to better graft survival.

2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

The following table summarizes the main findings from Studies 310 and 212.

	Study 310	Study 212
Basis of Evidence	Primary	Supportive
Design	Open label, controlled, randomized, non-IND	Open label, controlled, randomized, IND
Where Conducted	Europe, Canada, Australia	United States, Europe
Randomization Timepoint	At 3 months	Days 2 to 7
Primary Endpoint	Graft Survival	Renal Function
Secondary Endpoints (major)	Acute Rejection Renal function Efficacy failure Treatment Failure	Patient and Graft Survival Acute Rejection
Allografts	Primary or secondary	Primary only
Donors	Cadaver or living	Cadaver only
Numbers Enrolled		
Nonrandomized	95	49
Rapamune + CsA	215	97
Rapamune only	215	100
Graft Survival at 12 Months		
Rapamune +CsA	95.8%	92.8%
Rapamune only	97.2%	95.0%
	95% CI (-2.7, 5.5)	95% CI (-5.5, 9.9)
Acute Rejection (post CsA withdrawal)		
Rapamune +CsA	4.2%	6.2%
Rapamune only	9.8%	14.0%
	95% CI (0.3, 10.9)	95% CI (-1.5, 17.1)
Renal Function- Serum Creatinine (mol/mL)		
Rapamune +CsA	160.5 (4.3)	167.3 (9.2)
Rapamune only	147.0 (4.7)	126.0 (5.3)
	p <0.0001	p =0.0001

2.7 CONCLUSIONS AND RECOMMENDATIONS

The two studies submitted to provide evidence for a Rapamune treatment regimen with a withdrawal of CsA 2 to 4 months post randomization are supportive of one another. The results indicate that patient and graft survival 12 months post transplantation is high and equivalent between treatment regimens. In addition to the

high graft survival rates at 12 months, renal function at 12 months was significantly better for the patients who had CsA withdrawn and continued to receive Rapamune only compared to those who received Rapamune with CsA. However, there is an increase in acute rejections following CsA withdrawal. It cannot be determined from the data collected the type of patient who may be at higher risk for a rejection episode following CsA withdrawal and whether this is a clinically important event in terms of long-term graft survival. The data does indicate that renal function at 12 months for a patient who experiences an acute rejection during the first 12 months post-transplantation is reduced compared to those who do not experience an acute rejection. This reduction in renal function for patients who experience an acute rejection is evident regardless of treatment group. It is difficult to determine whether the short term improvement in renal function with CsA withdrawal, considering the increased incidence of an acute rejection following the withdrawal of CsA, will lead to long term graft survival without longer term follow-up data.

In addition, it is difficult to determine the patient population who may benefit from CsA withdrawal. The population studied is not entirely consistent with the current US kidney transplantation population. There were few blacks and other non-white populations studied and few living donor transplants studied. It is possibly easier to say who should not be considered for CsA withdrawal rather than say who should be considered for CsA withdrawal based on the current data.

Therefore, it is recommended that longer-term renal function and graft survival data be collected to determine the clinical impact of improved renal function on long-term graft survival. It is also recommended that patients more applicable to the US kidney transplant population be studied.

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/s/

Cheryl Dixon
3/6/02 05:30:01 PM
BIOMETRICS

Karen Higgins
3/6/02 05:38:24 PM
BIOMETRICS

Addendum to Statistical Review

To:	NDA 21-083/ SE1-006 Rapamune® (sirolimus) Oral Solution NDA 21-110/ SE1-004 Rapamune® (sirolimus) Tablets
From:	Cheryl Dixon, Ph.D. Biostatistician, Division of Biometrics III
Through:	Karen Higgins, Sc.D. Statistical Team Leader, Division of Biometrics III
Re:	Addendum to Statistical Review dated March 6, 2002
Date:	April 9, 2003

General

The original supplemental NDAs for Rapamune® (sirolimus) Oral Solution and Tablets were submitted April 6 and 16, 2001. These submissions contained studies that were conducted to provide efficacy and safety information on the use of Rapamune® within an immunosuppressive regimen that would allow for the elimination of cyclosporine 2 to 4 months after renal transplantation. The review of the studies that support this regimen can be found in the Statistical Review and Evaluation dated March 6, 2002.

On February 8, 2002, an approvable letter was sent to the applicant. This letter stated that additional information would be necessary to confirm the safety and efficacy of the requested regimen before the applications may be approved. The additional information included analysis of safety, acute rejection, patient and graft survival and the change in renal function over time up to 24 months post-transplantation in Study 310, addressing the impact of lost patients including disproportional discontinuation and dropout in the two arms of the studies, and completing post-marketing commitments regarding long-term information from studies that supported the original approval of Rapamune® and high risk patients.

On October 11, 2002, Wyeth Pharmaceuticals, Inc. submitted a response to the FDA Action Letter. Following this, on February 13, 2003, Wyeth submitted a 3-year Safety Summary for Study 310.

The remainder of this addendum will focus on long term follow-up data (through 36 months) from Study 310. Long-term data from Studies 301 and 302, which supported the original approval of Rapamune®, will be discussed briefly.

Study 310

The original supplemental NDAs provided information from Study 310 through 12 months post-transplantation. Data is now available through 36 months post-transplantation. The following table summarizes the 24 month and 36 month graft survival rates. The rates of graft survival are similar at both 24 and 36 months. However, the numerical difference in graft survival continues to increase through 36 months in favor of the Rapamune only group. Some of this difference may be explained by the slightly more cases of lost to follow-up in the Rapamune + CsA group which are included as failures in this analysis. However, when the lost to follow-up are treated as successes, the difference in graft survival rates is 4.6% with a 95% confidence interval of (-1.3, 10.5).

Table 1
Graft Survival through 24 and 36 months

	Rapamune + CsA (n=215)	**Rapamune** (n=215)	**Difference 95% CI**
Overall rate of graft survival at 24 months, n (%)	196 (91.2)	201 (93.5)	2.3 (-3.2, 7.8)
Reason for graft failure at 24 months			
Pure graft loss	9	5	
Death with a functioning graft	9	8	
Lost to follow-up	1	1	
Overall rate of graft survival at 36 months, n (%)	183 (85.1)	196 (91.2)	6.1 (-0.4, 12.6)
Reason for graft failure at 36 months			
Pure graft loss	15	7	
Death with a functioning graft	10	8	
Lost to follow-up	7	4	

*Difference is Rapamune – (Rapamune +CsA)
95% CI is calculated using the normal approximation to the binomial with continuity correction.

There were only 4 additional first biopsy-confirmed acute rejections seen between 12 and 36 months. Two acute rejections occurred between 12 and 24 months in the Rapamune + CsA group and 1 acute rejection occurred between 24 and 36 months in each group. The rates of acute rejection are not statistically significantly different between the two groups but there still remains an increased incidence of acute rejection post-randomization in the Rapamune only group.

Table 2
Acute Rejection through 36 Months

n (%)	**Rapamune + CsA** (n=215)	**Rapamune** (n=215)	**p-value***	**Difference, 95% CI**
Pre-randomization	20 (9.3)	22 (10.2)	0.871	0.9 (-5.2, 7.0)
Post-randomization**	12 (5.6)	22 (10.2)	0.107	4.6 (-0.9, 10.1)
Total	32(14.9)	44 (20.5)	0.164	5.6 (-2.1, 13.3)

*Fisher's Exact Test
** Including follow-up

Since the increased incidence of acute rejection following randomization was of concern, the Applicant was asked to determine any factors that may explain the increased incidence. The acute rejection data was analyzed by sex, living vs. cadaver donor, primary vs. secondary graft, presence or absence or delayed graft function, age of donor, donor ischemia time, patient age, number of human leukocyte antigen (HLA) mismatches, and use of antithymocyte globulin (ATG) or murine monoclonal antibody OKT3. Of these factors, differences between groups were only significant for HLA mismatches. Patients with a greater degree of HLA mismatch (> 3) in the Rapamune only group experienced a higher incidence of acute rejection post-randomization than those in the Rapamune + CsA group. It should be noted that this increased incidence of acute rejection was not associated with a detectable decrease in graft survival.

Table 3
Acute Rejection through 36 months by HLA Mismatch

n (%)	**Rapamune + CsA** (n=215)	**Rapamune** (n=215)	**p-value***
≤ 3			
Pre-randomization	13/148 (8.8)	12/142 (8.5)	1.000
Post-randomization**	10/148 (6.1)	11/142 (7.0)	0.823
Total	23/148 (15.5)	23/142 (16.2)	1.000
> 3			
Pre-randomization	7/67 (10.4)	10/72 (13.9)	0.610
Post-randomization**	2/67 (3.0)	11/72 (15.3)	0.018
Total	9/67 (13.4)	21/72 (29.2)	0.038

*Fisher's Exact Test
** Including follow-up

Renal function was assessed by serum creatinine and calculated Nankivell glomerular filtration rate (GFR). The following table presents the ITT analysis for serum creatinine and GFR at 6, 12, 24 and 36 months. The ITT analysis was performed on all available data whether or not the patient was receiving therapy. Following graft loss, GFR values were set to zero and serum creatinine values were treated as missing. The number of patients with missing data at the various time points was similar across treatment groups. The mean serum creatinine values for the Rapamune only group are significantly lower and the mean GFR values are significantly higher than those for the Rapamune + CsA group at all time points indicating improved renal function in patients who had CsA withdrawn. Renal function by HLA mismatch (data not shown) is similar to that seen for the overall population. This would indicate that despite a greater number of rejections in patients with > 3 HLA mismatches these patients also benefited from CsA withdrawal.

Table 4
Mean Serum Creatinine (μmol/L) and GFR (mL/min)
ITT analysis

		Rapamune + CsA (n=215)	Rapamune (n=215)	p-value*
Serum Creatinine				
	Month 6	162.5 ± 4.4** (188)***	152.0 ± 4.7 (192)	0.005
	Month 12	163.0 ± 4.8 (201)	147.4 ± 4.7 (199)	<0.001
	Month 24	171.7 ± 4.8 (187)	143.6 ± 5.1 (189)	<0.001
	Month 36	168.3 ± 5.0 (170)	145.4 ± 6.9 (183)	0.002
GFR				
	Month 6	55.4 ± 1.4 (189)	58.1 ± 1.3 (191)	<0.001
	Month 12	53.2 ± 1.5 (208)	59.3 ± 1.5 (203)	<0.001
	Month 24	48.4 ± 1.7 (203)	58.4 ± 1.6 (201)	<0.001
	Month 36	47.3 ± 1.8 (194)	59.4 ± 1.8 (194)	<0.001

*ANCOVA, covariate is last measurement before randomization (baseline)
** mean ± standard error
*** number of observations used to calculate mean

In addition to the ITT analysis, the Applicant performed on-therapy, completers, and last observation carried forward analyses. All three of these analyses support the results of the ITT analysis. These results show that renal function continues to improve over time for the Rapamune group that discontinued CsA and continues to deteriorate in patients who continue with CsA.

To further examine the trends of renal function over time, slope analyses were performed for 1/creatinine and GFR using a random coefficient regression analysis. Since CsA was fully discontinued by month 6, analyses were done over the 6 to 36 month period. All data between 6 and 36 months are included in the slope analysis. For patients with graft loss, a final value of zero was set to reflect the total loss of graft function and all data following the graft loss was deleted. The mean slopes were significantly negative for the Rapamune + CsA group and significantly positive for the Rapamune only group. The difference in slopes was also significant. These analyses confirm that the renal function slopes are divergent in favor of the Rapamune only group.

Table 5

Mean Slope 1/Creatinine (1/μmol per year) and GFR (mL/min per year)
6 to 36 months
ITT analysis

	Rapamune + CsA (n=215)	Rapamune (n=215)	Difference*
1/Creatinine			
Slope (mean ± SEM)	-0.433 ± 0.058 (205)**	0.247 ± 0.060 (195)	-0.680 ± 0.084
95% CI	(-0.548, -0.318)	(0.129, 0.365)	(-0.845, -0.515)
p-value***	<0.001	<0.001	<0.001
GFR			
Slope (mean ± SEM)	-3.631 ± 0.444 (204)	1.725 ± 0.455 (194)	-5.356 ± 0.636
95% CI	(-4.505, -2.757)	(0.829, 2.622)	(-6.608, -4.104)
p-value	<0.001	<0.001	<0.001

*(Rapamune + CsA) – Rapamune
**Number of patients used to calculate mean.
***Random coefficients regression model

The impact of rejection on renal function was also assessed. The following table summarizes renal function for patients who experienced acute rejection by when the rejection occurred with respect to randomization and for those who did not experience acute rejection. Patients who did not experience acute rejection or who had acute rejection pre-randomization benefited from CsA withdrawal. Patients with acute rejection after randomization had numerically better renal function in the Rapamune only group when compared to the Rapamune + CsA group. These patients also had the lowest renal function when compared to those who did not experience acute rejection and to those who had the acute rejection prior to randomization.

Table 6
Serum Creatinine (μmol/L) and GFR (mL/min) by Rejection Status
ITT analysis

		Rapamune + CsA (n=215)	Rapamune (n=215)	p-value*
Serum Creatinine				
Month 24	No rejection	167.4 ± 5.2** (163)***	134.7 ± 5.2 (152)	< 0.001
	Pre-randomization rejection	188.7 ± 13.7 (17)	144.8 ± 11.4 (20)	0.038
	Post-randomization rejection	229.8 ± 21.2 (7)	228.5 ± 22.8 (15)	0.880
Month 36	No rejection	164.4 ± 5.2 (150)	137.5 ± 7.7 (151)	0.001
	Pre-randomization rejection	177.3 ± 14.5 (14)	158.7 ± 14.7 (19)	0.428
	Post-randomization rejection	259.5 ± 36.1 (7)	211.6 ± 23.7 (14)	0.162
GFR				
Month 24	No rejection	51.4 ± 1.7 (172)	61.3 ± 1.7 (159)	<0.001
	Pre-randomization rejection	36.1 ± 5.4 (20)	56.3 ± 5.0 (21)	<0.001
	Post-randomization rejection	27.5 ± 7.1 (10)	35.9 ± 5.3 (19)	0.256
Month 36	No rejection	49.9 ± 1.9 (166)	62.6 ± 1.9 (158)	<0.001
	Pre-randomization rejection	36.6 ± 5.8 (18)	51.6 ± 5.7 (20)	0.028
	Post-randomization rejection	23.2 ± 6.6 (11)	39.5 ± 5.9 (17)	0.060

*ANCOVA, covariate is last measurement before randomization (baseline)
** mean ± standard error
*** number of observations used to calculate mean

Another concern at the time of the initial sNDAs was the significantly higher rate of discontinuations from study drug in the CsA elimination arm through 12 months. Therefore, the Applicant was asked to address the impact of lost patients including disproportionate discontinuation and dropout on the conclusions that may be made regarding the safety of the two regimens. In order to address these concerns, the Applicant presented various analyses including discontinuation tabulations listing the primary reason for discontinuation, time to discontinuation, demographic and baseline characteristics of discontinued patients, specific adverse events which lead to withdrawal, and selected laboratory data analyzed in several ways (ITT, on-therapy, completers, LOCF).

The following table summarizes the number of patients who discontinued treatment by 12, 24, and 36 months. As noted with the initial submission, more patients discontinued from the Rapamune only group in the first year. By the end of second year, the number of patients who discontinued was nearly identical. However, by the end of the third year,

the trend has reversed and more patients in Rapamune + CsA group have discontinued. Adverse events were the principal reason for discontinuation in both groups. Through 36 months, 21 patients in the Rapamune + CsA group and 10 patients in the Rapamune only group were converted to another Rapamune study after discontinuation.

Table 7
Number of patients who discontinued treatment

n (%)	Rapamune + CsA (n=215)	Rapamune (n=215)	p-value*
Through 12 months	38 (18)	58 (27)	0.027
Through 24 months	74 (34)	72 (33)	0.919
Through 36 months	103 (48)	81 (38)	0.041

*Fisher's Exact test

The following summarizes the remaining analyses used to explore whether discontinuations could have affected safety conclusions or introduced bias:

- There were no significant differences in demographic and baseline characteristics for patients who discontinued through month 24 between the two treatment groups.
- Adverse events that lead to discontinuation were quite varied. The only significant difference was more patients in the Rapamune + CsA group discontinued due to overdose (CsA toxicity).
- Results for laboratory parameters other than renal function were limited to on therapy and 30 days following discontinuation. The completers and LOCF analyses support the conclusions regarding the effects of treatment on laboratory parameters for the on-therapy analyses.

Therefore, there is no suggestion that lost patients or discontinuation has introduced important bias impairing safety conclusions regarding the comparison of the Rapamune + CsA group to the Rapamune with CsA withdrawal group.

Studies 301 and 302

Long-term information regarding graft and patient survival and renal function for Studies 301 and 302 has also been provided in this resubmission. Study 301 has follow-up data through 24 months and Study 302 has data through 36 months. For a complete discussion of these studies, see the Statistical Review and Evaluation of the original submission of NDA 21-083 dated August 20, 1999.

The following table summarizes graft survival at 24 months and 36 months for Studies 301 and 302, respectively. There were no significant differences in the rate of graft survival between the treatment groups in either study. Assessment of non-inferiority is not straightforward at these time points. The non-inferiority margin used for the primary time point of 12 months, 5%, may not be clinically relevant at these later times. In addition, the analyses presented are for the ITT population, which includes patients who are no longer on their randomized treatment. Therefore, it may be difficult to attribute late graft loss and deaths to the randomized treatment when the patient has not

been receiving that regimen for an extended period of time. In order to address this concern, an on-therapy analysis was requested from the Applicant. The analyses provided by the Applicant (data not shown) showed that graft survival was similar between treatment groups regardless of whether the patient was on-therapy or not and the on-therapy results were similar to the ITT results presented below. Furthermore, the percentages of patients on therapy were similar across treatment groups.

Table 8
Graft Survival for Study 301 at 24 months and Study 302 at 36 months
ITT Analysis

n (%)	Rapamune Oral Solution 2 mg	Rapamune Oral Solution 5 mg	Azathioprine	Placebo
Study 301	(n=284)	(n=274)	(n=161)	
Graft Survival	242 (85.3)	244 (89.1)	145 (90.1)	
Graft Loss	25 (8.8)	19 (6.9)	12 (7.5)	
Death	14 (4.9)	11 (4.0)	4 (2.5)	
Lost to Follow-up	3 (1.1)	0	0	
Difference* (95% CI)	-4.9 (-11.1, 1.4)	-1.0 (-6.9, 4.9)		
Study 302	(n=227)	(n=219)		(n=130)
Graft Survival	184 (81.1)	175 (79.9)		105 (80.8)
Graft Loss	24 (10.6)	27 (12.3)		14 (10.8)
Death	19 (8.4)	15(6.9)		10 (7.7)
Lost to Follow-up	0	2 (0.9)		1 (0.8)
Difference (95% CI)	0.3 (-8.2, 8.8)	-0.9 (-9.5, 7.8)		

*Rapamune - Control

The following tables summarize long term renal function for Studies 301 and 302. Table 9 summarizes the mean values for serum creatinine and GFR. Table 10 summarizes the slope analyses (as described in Study 310) for 1/ serum creatinine and GFR. The slope analyses were done over the 6 to 24 month period for Study 301 and the 6 to 36 month period for Study 302. As can be seen from both tables, patients who receive the combination of Rapamune with CsA continue to demonstrate decreased renal function in comparison to the control groups and this decreased renal function continues to increase over time. In most situations, however, the decrease in renal function is not statistically significantly different from the control.

Table 9

Mean Serum Creatinine (µmol/L) and GFR (mL/min)

ITT analysis

		Rapamune 2 mg	Rapamune 5 mg	Azathioprine	Placebo
Serum Creatinine					
Study 301	Month 24	(n=284) 171.5 ± 5.8* (211)** p=0.119***	(n=274) 189.3 ± 8.0 (215) p=0.007	(n=161) 156.4 ± 8.0 (130)	
Study 302	Month 36	(n=227) 181.6 ± 8.9 (160) p=0.119	(n=219) 186.3 ± 8.4 (152) p=0.119		(n=130) 148.9 ± 5.3 (88)
GFR					
Study 301	Month 24	(n=284) 58.4 ± 1.5 (221) p=0.110	(n=274) 52.6 ± 1.5 (222) p<0.001	(n=161) 64.2 ± 1.9 (132)	
Study 302	Month 36	(n=227) 48.1 ± 1.8 (183) p=0.094	(n=219) 46.1 ± 2.2 (177) p=0.033		(n=130) 53.4 ± 2.7 (102)

*mean ± standard error

**Number of patients used to calculate mean

***ANCOVA Rapamune vs. Control

Table 10

Mean Slope 1/Creatinine (1/μmol per year) and GFR (mL/min per year)
ITT analysis

	Rapamune 2 mg	Rapamune 5 mg	Azathioprine	Placebo
1/Creatinine				
Study 301 (6 to 24 months)	(n=284)	(n=274)	(n=161)	
Slope (mean ± SEM)	-0.43 ± 0.14	-0.39 ± 0.11	-0.30 ± 0.14	
	275*	253	151	
95% CI	(-0.64, -0.23)	(-0.59, -0.18)	(-0.57, -0.04)	
p-value**	0.449	0.616		
Study 302 (6 to 36 months)	(n=227)	(n=219)		(n=130)
Slope (mean ± SEM)	-0.32 ± 0.07	-0.26 ± 0.07		-0.17 ± 0.09
	209	200		114
95% CI	(-0.45, -0.18)	(-0.40, -0.12)		(-0.30, 0.07)
p-value	0.084	0.226		
GFR				
Study 301 (6 to 24 months)	(n=284)	(n=274)	(n=161)	
Slope (mean ± SEM)	-3.5 ± 0.8	-3.1 ± 0.8	-1.8 ± 1.1	
	275	253	151	
95% CI	(-5.1, -1.9)	(-4.7, -1.4)	(-3.9, 0.3)	
p-value	0.194	0.339		
Study 302 (6 to 36 months)	(n=227)	(n=219)		(n=130)
Slope (mean ± SEM)	-2.6 ± 0.5	-2.4 ± 0.6		-1.1 ± 0.7
	209	200		114
95% CI	(-3.6, -1.5)	(-3.5, -1.3)		(-2.6, 0.3)
p-value	0.118	0.165		

*Number of patients used to calculate mean
**Random coefficients regression model Rapamune vs. Control

Summary

The Rapamune with CsA withdrawal regimen maintains high patient and graft survival. There is a slight increased incidence of acute rejection with this regimen. Most of these episodes of acute rejection occurred during the first 3 months following CsA withdrawal.

Long-term renal function data from Studies 301 and 302, in which patients received the Rapamune + CsA combination, continue to demonstrate decreased renal function compared to control therapies. The results from Study 310 show that the long-term renal function of patients on Rapamune following CsA withdrawal is superior to that of patients who continue to receive the Rapamune + CsA combination.

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/s/

Cheryl Dixon
4/9/03 03:26:49 PM
BIOMETRICS

Karen Higgins
4/9/03 03:43:07 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **21-083 SE1 006, 21-110 SE1 004**	Submission Date(s): **4/6/01, 10/11/02**
Brand Name	**Rapamune**
Generic Name	**Sirolimus**
Primary Reviewer	**Jang-Ik Lee, Pharm.D., Ph.D.**
Pharmacometrics Reviewer	**Frank Pelsor, Ph.D.**
Team Leader	**Philip Colangelo, Pharm.D., Ph.D.**
OCPB Division	**DPE III (HFD-880)**
OND Division	**ODE IV DSPIDP (HFD-590)**
Sponsor	**Wyeth Pharmaceutical, Inc.**
Relevant IND(s)	**55, 322**
Submission Type; Code	**Major amendment of efficacy supplements; AZ**
Formulation; Strength(s)	**Oral solution; 1 mg/mL (N21-083)** **Tablet; 1, 2, and 5 mg (N21-110)**
Indication	**Prophylaxis of organ rejection in patients receiving renal transplants**

Dosage and Administration

- *De novo transplant patients*: **a daily oral maintenance dose of 2 mg with a loading dose of 6 mg in combination with cyclosporine and corticosteroids**
- *Stable patients (2 - 4 months post transplant) at low to moderate immunological risk with cyclosporine withdrawal*: **a daily dose to maintain whole blood trough concentrations of 12 - 24 ng/mL (chromatographic method)**

1. EXECUTIVE SUMMARY

This is a Clinical Pharmacology and Biopharmaceutics (CPB) review for the supplemental NDAs pursuing an approval of a sirolimus maintenance regimen in which cyclosporine is gradually withdrawn from a triple immunosuppressive regimen consisting of sirolimus, cyclosporine, and corticosteroids 2 - 4 months after renal transplantation. The sponsor originally submitted these sNDAs on 4/6/01 and Dr. Kofi Kumi reviewed their CPB part (refer to the CPB review dated 5/15/02 in DFS). Based on his review, the Agency requested to the sponsor to define a therapeutic sirolimus concentration range for therapeutic drug monitoring (TDM) for the sirolimus maintenance regimen in the approvable letter dated 2/8/02. In reponse to the request, the sponsor resubmitted these sNDAs with additional data collected from an ongoing study (310). This resubmission also contains reports for Phase IV commitments stated in the approval letter of the original Rapamune NDAs.

The objectives of this review are (1) to address the issues regarding the therapeutic sirolimus concentration range for TDM as proposed by the sponsor and (2) to assess the consistency of the additional data in comparison with the data provided in the previous submission. Dr. Frank Pelsor, a CPB reviewer, is currently working on a pharmacometrics review regarding the Phase IV commitments and will complete his review separately.

1.1. Recommendation

The reviewer concurs with Dr. Kofi Kumi's previous CPB review (refer to the CPB review dated 5/15/02 in DFS) in that therapeutic drug monitoring (TDM) for sirolimus dosing is feasible in renal transplant patients under a concentration-controlled sirolimus maintenance regimen with cyclosporine withdrawal 2 - 4 months post-transplantation. Although the therapeutic concentration range and the maximum tolerated concentration of sirolimus was not adequately defined, the whole blood steady state trough concentration of sirolimus at the range of 15 - 30 ng/mL by immunoassay (12 - 24 ng/mL by chromatographic assay) that the sponsor proposed based on the 24-month report of Study 310 is an acceptable target concentration range for sirolimus TDM. The current maximum commercial capacity of sirolimus assay for TDM in the United States is >1600 samples per day and appears to be ready to expand. Overall, from a CPB standpoint, this reviewer recommends the proposed concentration range as an acceptable target for sirolimus TDM for the sirolimus maintenance regimen with cyclosporine withdrawal.

1.2. Comments Conveyed to the Sponsor

Please complete Study 310 as planned and provide further evaluation of the relationship(s) between sirolimus whole blood trough concentrations and the relevant efficacy and safety variables upon completion of the study.

_____ Date: _____

Jang-Ik Lee, Pharm.D., Ph.D.
Pharmacokinetics Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Philip Colangelo, Pharm.D., Ph.D. _____ Date: _____

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3. SUMMARY OF CPB FINDINGS

The sponsor proposed, based on the results from a Phase III efficacy and safety study (310), a sirolimus trough concentration range of 15 - 30 ng/mL by immunoassay (12 - 24 ng/mL by chromatographic assay) as a target concentration range for sirolimus therapeutic drug monitoring (TDM) in renal transplant patients whose cyclosporine has been gradually withdrawn 2 - 4 months post-transplantation. The sponsor explored a maximum tolerated concentration of sirolimus (approx. 15 - 20 ng/mL by chromatographic assay) in two previous phase II pilot studies, which was considered to be preliminary information. Provided the safety profile observed in Study 310 is clinically acceptable, the proposed range appears to be at or below the maximum tolerated concentration of sirolimus.

Given the overall clinical outcome of the first two years of Study 310 (See Dr. Arturo Hernandez's clinical review), the target range is acceptable for sirolimus TDM. The time-normalized whole blood steady state trough concentration ($C_{min,TN}$) of sirolimus observed in renal transplant patients under the concentration-controlled sirolimus maintenance regimen with cyclosporine withdrawal (Group B) over the time intervals studied corresponded with the respective target concentration ranges (Table1). Table 1 shows the time-normalized steady state doses ($Dose_{TN}$) of sirolimus, and the percentages of patients below, within, and above the target concentration ranges during the treatment intervals. The sirolimus $C_{min,TN}$ observed in patients under the fixed-dose sirolimus maintenance regimen with cyclosporine coadministration (Group A) appears to be at steady state throughout the study period after randomization. A comparison of the sirolimus $C_{min,TN}$ values observed in Group A yielded very similar ranges between the two intervals (Table1).

Table 1. Time-normalized steady state doses ($Dose_{TN}$) and time-normalized whole blood steady state trough concentrations ($C_{min,TN}$) of sirolimus observed from renal transplant patients under fixed-dose sirolimus maintenance regimen with cyclosporine coadministration (Group A) and concentration-controlled sirolimus maintenance regimen with cyclosporine withdrawal (Group B)

	Group A		Group B	
Study Interval	137 – 386 days	387 – 763 days	137 – 386 days	387 – 763 days
$Dose_{TN}$ (mg/day)				
Mean ± SD	2.1 ± 0.7	2.0 ± 0.8	8.2 ± 4.2	6.4 ± 3.0
10^{th} – 90^{th} Percentile	NA	NA	3.8 -13.3	3.3 – 10.0
Target C_{min} Range (ng/mL)	NA	NA	20 - 30	15 - 25
Observed $C_{min,TN}$ (ng/mL)				
Mean ± SD	10.7 ± 3.8	11.2 ± 4.1	23.3 ± 5.0	22.5 ± 4.8
10^{th} – 90^{th} Percentile	6.5 – 15.0	6.7 – 16.6	16.9 – 29.4	16.1 – 27.8
Patients below Target C_{min}	NA	NA	29.3 %	8.7 %
Patients within Target C_{min}	NA	NA	61.6 %	70.1 %
Patients above Target C_{min}	NA	NA	9.2 %	21.3 %

NA, not applicable

In comparison of the variability of $C_{min,TN}$ values of sirolimus, the coefficients of variation (CV) for the concentration-controlled maintenance regimen was smaller than the CVs for the fixed-dose maintenance regimen as expected. Whereas the respective CVs of the $C_{min,TN}$ values for

Group A were 36% (mean ± SD, 10.7 ± 3.8 ng/mL) and 37% (11.2 ± 4.1 ng/mL) during the intervals of 137 - 386 and 387 - 763 days, the respective CVs for Group B were 22% (23.3 ± 5.0 ng/mL) and 21% (22.5 ± 4.8 ng/mL).

The performance of sirolimus analytical methods reported in this resubmission was not different from the performance previously reported in Dr. Kofi Kumi's review (refer to the CPB review dated 5/15/02 in DFS), and corresponds with the recommended performance in the Agency's Guidance for Bioanalytical Method Validation.

4. QUESTION-BASED REVIEW

4.1. Sponsor's Response to the Approvable Letter of Efficacy Supplements (2/8/02)

Item No. 6: Define a therapeutic concentration range for sirolimus therapeutic drug monitoring in renal transplant patients whose cyclosporine has been eliminated by providing data and analyses that support this range and identifies the efficacious and maximum tolerated (safe) concentration

Based on the results from an ongoing Phase III efficacy and safety study (310), the sponsor proposed a sirolimus trough concentration range of 15 - 30 ng/mL by immunoassay (12 - 24 ng/mL by chromatographic assay) as a target concentration range for sirolimus TDM in renal transplant patients whose cyclosporine has been withdrawn 2 - 4 months post-transplantation. Given the overall clinical outcome of the first two years of Study 310 (See Dr. Arturo Hernandez's clinical review), the target range is acceptable. However, the therapeutic concentration range of sirolimus was not adequately defined. The sponsor explored the maximum tolerated concentration of sirolimus (approx. 15 - 20 ng/mL by chromatographic assay) in two phase II pilot studies, which was considered to be preliminary information. The sponsor is encouraged to assess the relationship between sirolimus trough concentrations and the relevant safety and efficacy variables upon completion of Study 310.

How is Study 310 conducted and analyzed?

The study was initiated in 525 patients with *de novo* renal transplant at 57 transplant centers in Europe, Canada, and Australia. After a prestudy screening period of 3 months ± 2 weeks, 430 patients were randomly assigned to Group A or B. During the screening period, all patients received cyclosporine doses to attain whole blood trough concentrations of cyclosporine at a range of 200 - 400 ng/mL through Month 1 and 150 - 300 ng/mL from Month 1 until the random assignment. All patients also received oral sirolimus maintenance doses of 2 mg/day until the random assignment. Sirolimus dose was given 4 hours after the morning dose of cyclosporine. Corticosteroids were initially administered as per local standard practice and tapered to a dose of 5 - 10 mg/day from Month 6.

After randomization, the patients in Group A continued to receive cyclosporine doses to maintain cyclosporine trough concentrations at a range of 150 - 250 ng/mL for 4 - 6 weeks and 75 - 150 ng/mL thereafter. The patients in Group A also continued to receive the nominal maintenance dose of sirolimus (2 mg/day) throughout the study. For the patients in Group B, cyclosporine doses were gradually withdrawn over 4 - 6 weeks and sirolimus doses were adjusted to maintain sirolimus trough concentrations at a range of 20 - 30 ng/mL for the first year and 15 - 25 ng/mL after the first year treatment. Sirolimus exposure was assessed by statistical averaging and area methods. Average doses and trough concentrations in individual patients were obtained by calculating time-normalized dose at steady state ($Dose_{TN}$) and time-normalized whole blood trough concentration at steady state ($C_{min,TN}$), respectively, across days according to the following relationships:

$Dose_{TN} = AUD_{0-t} / t$
$C_{min,TN} = AUC_{0-t} / t$

where	AUD_{0-t}:	area under the dose-time curve from the start of dose administration to time t in a slot interval of measurement
	AUC_{0-t}:	area under the trough concentration-time curve from the start of dose administration to time t in a slot interval of measurement
	t:	time in a slot interval of measurement

How were sirolimus concentrations monitored and sirolimus doses adjusted in Study 310?

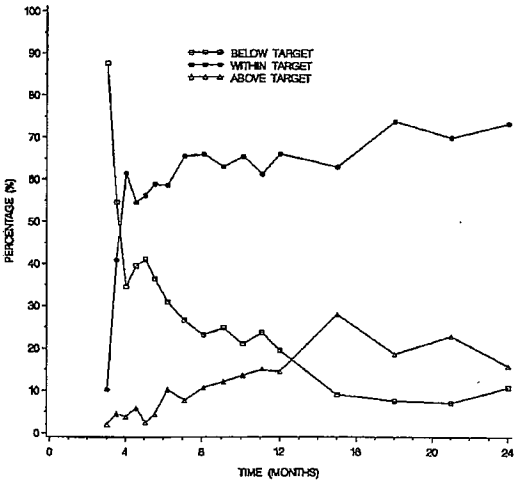
For both groups, the whole blood trough concentrations of sirolimus were monitored within 3 days after transplantation, within a day after hospital discharge, monthly through Month 12, and every 3 months thereafter. In addition, for Group B only, the concentrations were monitored weekly for the first four weeks following random assignment and every two weeks for the next 2 months. The concentrations were determined by immunoassay using IMx analyzer or chromatographic methods but expressed in immunoassay or equivalent results (**see 4.2 Analytical**).

Before randomization, sirolimus doses were not adjusted unless the patient's whole blood trough concentration had been < 5 ng/mL. After randomization, for Group A, sirolimus doses were the same as the doses before randomization. For Group B, when the whole blood trough concentration of sirolimus was < 20 ng/mL (from randomization to Month 12) or < 15 ng/mL (thereafter), a new maintenance dose [current maintenance dose x desired trough (i.e., 25 ng/mL for the first year) / current trough] was administered. A loading dose [3 x (new maintenance dose - current maintenance dose)] was administered in addition to a new maintenance dose when considerable increase in sirolimus trough concentration was necessary. When an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading dose was administered over 2 days. When the concentration was at the range of 20 - 30 ng/mL, sirolimus dose was not adjusted. When the concentration was > 30 ng/mL (from randomization to Month 12) or > 25 ng/mL (thereafter), a new maintenance dose was calculated and administered.

How well did Study 310 adhere to the target trough concentrations of sirolimus? Were the observed trough concentrations well within the target concentrations?

The $C_{min,TN}$ observed in the majority of patients in Group B nearly approached the target sirolimus trough concentration ranges of 20 - 30 and 15 - 25 ng/mL during the intervals of 137 - 386 and 387 - 763 days, respectively. Figure 1 demonstrates the percentage of patients with sirolimus $C_{min,TN}$ below, within, and above the target ranges. The percentage was based on the number of patients at each given slot interval of measurement because some patients withdrew or had acute rejections that warranted discontinuation of study drug treatment. The trend in Figure 1 suggests

Figure 1. Percentage of renal allograft patients within, below, and above the target concentration ranges of sirolimus for Group B



relatively large inter-slot variabilities. However, a large proportion of patients was within the target concentration ranges from a month after randomization.

Table 2 provides the percentages of the sirolimus $C_{min,TN}$ within, below, and above the target concentration ranges. Patients who were within the two ranges showed low inter-slot variabilities (range of coefficient of variation [CV], 6.6 - 7.1%) compared with patients who were either below or above the target range (range of CV, 19.3 - 48.7%).

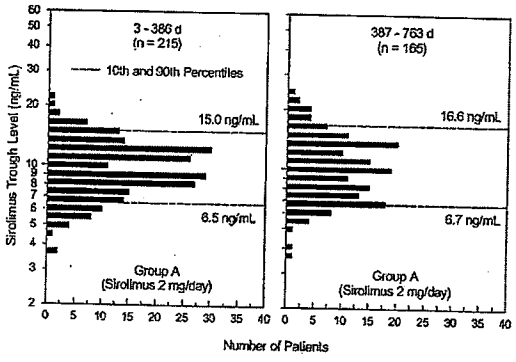
Table 2. Mean percentages of patients below, within, and above the target concentration ranges of sirolimus after renal transplantation

4 - 12 Months Post-Transplantation		13 - 24 Months Post-Transplantation	
Concentration Range	Mean % (CV %)	Concentration Range	Mean % (CV %)
< 20 ng/mL	29.3 (26.2)	< 15 ng/mL	8.7 (19.3)
20 to 30 ng/mL	61.6 (6.6)	15 to 25 ng/mL	70.1 (7.1)
> 30 ng/mL	9.2 (48.7)	> 25 ng/mL	21.3 (24.8)

In the renal allograft patients who stayed on cyclosporine coadministration, what were the actual trough concentration ranges of sirolimus observed?

The mean ± SD $C_{min,TN}$ values of sirolimus observed in Group A were 10.7 ± 3.8 and 11.2 ± 4.1 ng/mL during the intervals of 137 - 386 and 387 - 763 days, respectively. The mean values were slightly larger than the values with same dosing regimen in current sirolimus labeling (9.5 ± 3.9 ng/mL). The respective mean $Dose_{TN}$ values of sirolimus were 2.1 ± 0.7 and 2.0 ± 0.8 mg/day. The $C_{min,TN}$ appears to be at steady state throughout the study period after randomization (data not shown). Figure 2 demonstrates the frequency distributions of the $C_{min,TN}$ values observed in Group A over 2 years. A comparison of the 10^{th} - 90^{th} percentiles for the sirolimus $C_{min,TN}$ yielded very similar ranges over the intervals of 137 - 386 and 1 (6.5 - 15.0 ng/mL) and 387 - 763 days (6.7 - 16.6 ng/mL).

Figure 2. Distribution frequencies of the time-normalized steady-state trough concentrations ($C_{min,TN}$) of sirolimus in renal allograft patients in Group A



Is the TDM plan acceptable?

This question needs to be answered based on both CPB and clinical reviews. Provided the efficacy and safety of the concentration-controlled sirolimus maintenance regimen with cyclosporine withdrawal (Group B) is comparable to or more favorable than the efficacy and safety of the fixed-dose sirolimus regimen with cyclosporine coadministration (Group A), the proposed concentration range for sirolimus TDM is considered to be acceptable since the

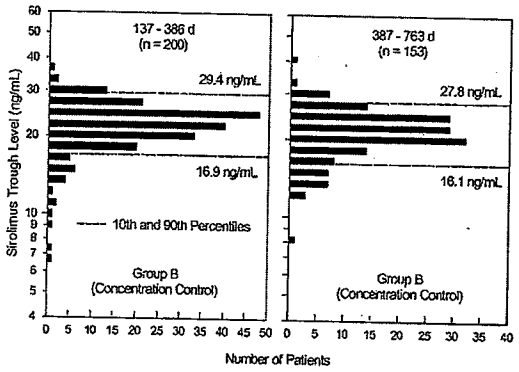
majority of the patients in Group B had trough concentrations within the targeted range (see below).

According to the reviewing medical officer's (Dr. Arturo Hernandez) efficacy review, patient and graft survival for intent-to-treat population (> 90%) was similar between Groups A and B at 24 months, and comparable to the national standards. According to protocol statistical parameters, Group B reached non-inferiority compared with Group A. Biopsy-confirmed acute rejection episodes were mild to moderate and the differences between Groups A and B were not statistically significant. Severe acute rejections did not occur following randomization.

According to Dr Hernandez's safety review, 48% of patients from Group A and 38% from Group B ($p = 0.041$) discontinued treatment at 36 months follow-up. Abnormal kidney function and cyclosporine toxicity were the main adverse events that lead to discontinuation in Group A, while abnormal liver function tests and dyslipidemias were the principal adverse events for discontinuation in Group B. The incidence of treatment-emergent adverse events in Group B was significantly higher for thrombocytopenia, hypokalemia, increased liver transaminases, ileus, and abnormal healing compared with Group A. On the other hand, there were significantly fewer cases of cyclosporine toxicity, hypertension, hyperuricemia, creatinine elevation, edema, cataract, abnormal kidney function, and toxic nephropathy in Group B. Pneumonia was more frequent in Group B while herpes zoster was more frequent in Group A. Other types of infections were similar in both groups. Group B presented fewer malignancy rates at 24 months (9.8% *versus* 4.2%, $p = 0.036$). Renal function was significantly better in Group B. Group B also showed lower serum uric acid, phosphorus, potassium, and higher serum magnesium than Group A. The cholesterol and triglyceride levels were significantly higher in Group B. Serum aminotransferases and LDH presented significantly higher mean values in Group B. Mean systolic and diastolic blood pressures were significantly better in Group B from 6 through 36 months follow up.

The respective mean ± SD values of the sirolimus $C_{min,TN}$ in Group B were 23.3 ± 5.0 and 22.5 ± 4.8 ng/mL during the intervals of 137 - 386 and 387 - 763 days (Table 1). The respective mean $Dose_{TN}$ values were 8.2 ± 4.2 and 6.4 ± 3.0 mg/day. Figure 3 demonstrates the frequency distributions of the sirolimus $C_{min,TN}$ values. A comparison of the 10^{th} - 90^{th} percentiles of the values yielded very similar ranges over the time intervals of 137 - 386 (16.9 - 29.4 ng/mL) and 387 - 763 days (16.1 - 27.8 ng/mL) although the target was different. The 10^{th} - 90^{th} percentiles nearly approached the recommended target concentration ranges of 20 - 30 ng/mL and 15 - 25 ng/mL, respectively. The respective 10^{th} - 90^{th} percentiles of sirolimus $Dose_{TN}$ were 3.8 - 13.3 mg/day and 3.3 - 10.0 mg/day during the intervals of 137 - 386 days and 387 - 763 days.

Figure 3. Distribution frequencies of the time-normalized steady-state trough concentrations ($C_{min,TN}$) of sirolimus in renal allograft patients in Group B



In a Phase II study (212) that was conducted with a similar design to Study 310, the 10^{th} - 90^{th} percentiles of the trough concentrations were similar (12.2 - 24.9 ng/mL by immunoassay) over the time interval of 32 - 386 days although the target range was lower (10 - 20 ng/mL, refer to Dr. Kumi's CPB review dated 5/15/02 in DFS).

In comparison of the CV of $C_{min,TN}$ values, the concentration-controlled maintenance regimen of sirolimus showed smaller variability than the fixed-dose maintenance regimen. Whereas the CVs for Group A were 36% (mean ± SD, 10.7 ± 3.8 ng/mL) and 37% (11.2 ± 4.1 ng/mL), the respective CVs for Group B were 22% (23.3 ± 5.0 ng/mL) and 21% (22.5 ± 4.8 ng/mL) during the intervals of 137 - 386 and 387 - 763 days, respectively. The comparison of the variability of $Dose_{TN}$ values showed opposite results as expected. Whereas the respective CVs of the $Dose_{TN}$ values for Group A during the intervals were 35% (2.1 ± 0.7 mg/day) and 39% (2.0 ± 0.8 mg/day), the respective CVs for Group B were 51% (8.2 ± 4.2 mg/day) and 47% (6.4 ± 3.0 mg/day).

Overall, Study 310 demonstrated that a sirolimus maintenance regimen with cyclosporine withdrawal at 2 - 4 months post-transplantation with a concentration-controlled TDM plan achieved sirolimus trough concentrations at an approximate range of 15 - 30 ng/mL (immunoassay). Given the large variability in the oral clearance of sirolimus (CV, 40 - 65% in current sirolimus labeling), a fixed-dose regimen for sirolimus-based therapy without a calcineurin inhibitor would be anticipated to result in a wider range of trough concentrations, which increases the risk of both under- and over-immunosuppression. Therefore, a TDM for the sirolimus maintenance regimen is expected to reduce the risk.

What is the maximum tolerated trough concentration of sirolimus?

The maximum tolerated trough concentration of sirolimus remains to be adequately determined. Provided the safety profile observed in Study 310 is clinically acceptable, the study was likely conducted at or below the maximum tolerated concentration.

The sponsor explored the maximum tolerated trough concentration of sirolimus in two phase II pilot studies (207 and 210) that were conducted to investigate the efficacy and safety of a sirolimus-based therapy in comparison with a cyclosporine-based therapy in patients with *de novo* renal transplantation. Based on the sponsor's summary, an average trough concentration of 30 ng/mL (chromatographic assay) during the first 2 months resulted in a rate of acute rejection > 20% with marked sirolimus concentration-related toxic effects. Mild sirolimus-related toxicity was still evident even after the average sirolimus trough concentration was reduced to 15 - 20 ng/mL at a subsequent maintenance period. However, the investigators considered the average concentration to be clinically acceptable for sirolimus maintenance in light of the improved renal function as compared with the clinical outcome observed in the cyclosporine-based therapy. Based on the results of the two studies, the sponsor considers 15 - 20 ng/mL by chromatographic assay (approx. 19 - 25 ng/mL by immunoassay) as the maximum tolerated trough concentration of sirolimus during maintenance administrations. Dr. Kofi Kumi briefly reviewed and considered the results of these two studies to be preliminary information.

4.2. Analytical

What methods have been used for sirolimus assay?

What was the performance of the sirolimus assay methods used for CPB studies in this resubmission?

Dr. Kofi Kumi reviewed the analytical methods used for CPB studies during the review of the first submissions of these supplements (refer to the CPB review dated 5/15/02 in DFS). This reviewer reviewed the updated part of the CPB studies including updated analytical performance. The performance of analytical methods in this resubmission (Table 3) was essentially the same as the performance in Dr. Kumi's review and corresponds with the recommended performance in the Agency's Guidance for Bioanalytical Method Validation.

Through December 1999, by which time all patients enrolled in Study 310 had been treated for at least 6 months, whole blood sirolimus concentrations were determined at local or central laboratories using an MEIA with an IMx analyzer. After December 1999, blood samples were analyzed by validated HPLC-MS/MS or HPLC-UV methods. Out of the 12,061 samples included in this 24-month report, 3871 blood samples (32.1%) were analyzed by one of the non-IMx methods.

Table 3: Summary of the performance of whole blood sirolimus assays used in Study 310

	IMx	HPLC/MS/MS I	HPLC/MS/MS II	HPLC/UV
Linear range (ng/mL)				
Limit of quantitation (ng/mL)	1.5	0.2	1	2.5
Accuracy	Relative error (%)			
Intraday	4.3 to 6.1			-4.8 to -0.2
Interday	1.1 to 2.2	-4.8 to -2.0	-0.6 to 3.7	-4.8 to 4.2
Precision	Coefficient of variation (%)			
Intraday	2.8 to 7.4	7.5 to 9.2	1.9 to 7.3	12.0 to 14.4
Interday	5.5 to 8.3	1.1 to 4.2	3.0 to 8.1	2.6 to 13.0

What is the current availability of sirolimus assays for TDM?

[redacted]

Commercial Laboratories

[redacted]

sponsor are advertising the availability of the assay in transplant journals and direct mail as well as sales force promotion.

[redacted]

sirolimus assay.

Individual Transplantation Centers

Since the approval of Rapamune in 1999, clinical laboratories in a number of transplant centers have established 'in-house' assay methods for sirolimus TDM using either an HPLC-UV or LC-

[redacted]

The Sponsor

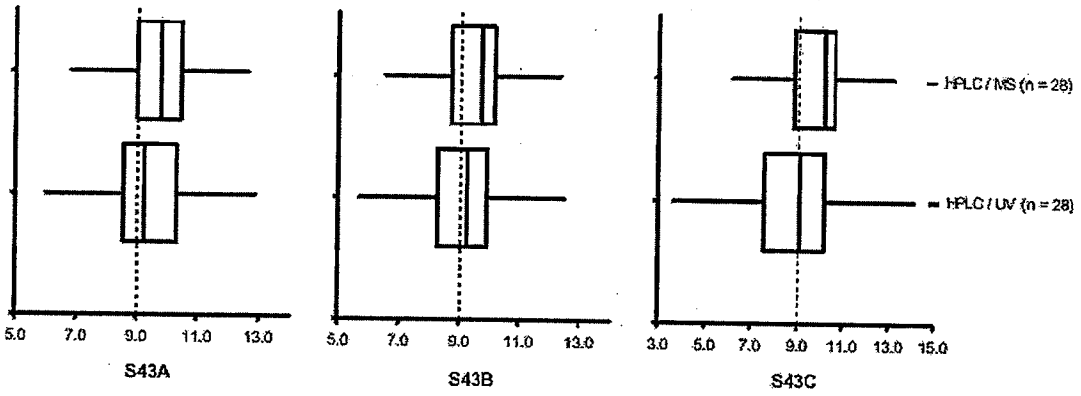
To make available an easy-to-use automated platform assay for sirolimus TDM, the sponsor made an agreement wi[redacted]latform assay may be available in late 2003. In addition, the sponsor provides technical support for sirolimus assay to individual laboratories that is associated with transplant centers requesting such support. The support includes enrollment information on a proficiency test program, sirolimus prescribing information, and a CD-ROM, which provides a technical aspect of sirolimus assays. The sponsor also provides internal and reference standards under a materials transfer agreement.

Proficiency Testing

The proficiency testing for sirolimus assay from [redacted]en split into two main functions. The first function (Prestudy Proficiency Testing) is to ensure that participating laboratories are proficient in performing sirolimus assay. The test consists of 78 blinded samples packaged as 5 sets of samples, which the laboratories are required to assay over five separate days. The data generated in this test provide information on intra- and inter-day precision and accuracy, specificity, and linearity. The second function (Ongoing Proficiency Testing) is to document ongoing proficiency of these laboratories in performing sirolimus assay. The test consists of three blinded samples sent to each laboratory every month. These samples

are to be assayed with a batch of regularly scheduled samples. The data generated in a laboratory are compared with those generated by other laboratories using the same technique. Figure 4 graphically demonstrates a result of an Ongoing Proficiency Testing for three sirolimus samples made from an aliquot of sirolimus-free blood to which sirolimus was added to produce a final concentration of 9.0 ng/mL. The number of participants were 32 as of July 2001. Information on the proficiency testing can be found at www.bioanalytics.co.uk. The College of American Pathologists initiated a proficiency testing program for sirolimus in the year 2001. This program provides two whole blood specimens three times a year.

Figure 4. A monthly proficiency testing result conducted by
(The line across the box is the median. The upper and lower edges of the box are the 25th and 75th percentiles. The whiskers join the highest and lowest values that occur in the regions 1.5x the interquartile range above and below the third and first quartiles)



4.3. Miscellaneous Questions

What is the current status of sirolimus TDM?

TDM for sirolimus dosing appears to be widely used in the United States although the current sirolimus labeling recommends monitoring sirolimus trough concentrations only in special circumstances such as hepatic impairment and concomitant use of inducers/inhibitors of cytochrome P450 enzymes. In a survey conducted by Hase/Schannen Research Associates in January 2001 to 25 transplant surgeons and 19 nephrologists from 35 of the top 100 major transplant centers in the United States, 37 participants (84%) indicated that they monitored sirolimus concentrations for their patients on a sirolimus regimen. In a more recent survey conducted by Hase/Schannen in June 2002 to transplant surgeons and nephrologists who have greater than 5 patients on Rapamune and attended the 2002 American Transplant Congress, 28 of 30 interviewees (93%) utilized TDM for sirolimus dosing.

8 Page(s) Withheld

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Withheld Track Number: Clin Pharm/Bio- 1a

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Jang-Ik Lee
4/11/03 01:48:48 PM
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Phil Colangelo
4/11/03 05:27:19 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-083 SE1-006

21-110 SE1-004

Submission Dates: 4/06/01, 4/8/01, 4/16/01, 12/8/01, 12/18/01, 12/21/01, 1/8/02, 1/11/02, 1/22/02

Generic Name, Strength and Formulation: Sirolimus (Rapamycin) 1 mg/mL Oral Solution and 1mg tablet

Brand Name: Rapamune®

Applicant: Wyeth Ayerst Research

Proposed Indication: Prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune be used initially in a regimen with CsA and corticosteroids. CsA withdrawal should be considered 2 to 4 months after transplantation

Submission Type: Efficacy Supplement (1S)

OND Division: Special Pathogen and Immunologic Drug Products (DSPIDP, HFD-590)

OCPB Division: Pharmaceutical Evaluation III (DPEIII, HFD-880)

Reviewer: Kofi A. Kumi, Ph.D.

Team Leader: Funmi Ajayi, Ph.D.

Secondary Reviewer: Arzu Selen, Ph.D.

Final Review Date: 2/6/02

Executive Summary

This supplemental New Drug Application (sNDA) contained data to support a Rapamune Maintenance Regimen (RMR) in which Cyclosporine (CsA) is eliminated from the maintenance regimen after 2-4 months of triple immunosuppressive therapy of sirolimus, CsA and corticosteroids. Trough sirolimus concentration profiling was conducted in studies in order to 1) characterize the pharmacokinetic behavior of sirolimus during concomitant administration with CsA and corticosteroids and after withdrawal of CsA from the regimen and 2) to determine the therapeutic window of sirolimus during a maintenance regimen after withdrawal of CsA. Sirolimus (Rapamune®) is currently approved for prophylaxis of organ rejection in patients receiving renal transplants. Currently, it is recommended that Rapamune be used in a regimen with CsA and corticosteroids

The sponsor demonstrated that therapeutic drug monitoring is feasible for sirolimus. Mean (%CV) sirolimus trough concentration was 10.8 (36) ng/mL during concomitant administration with CsA and corticosteroids and 23.3 (22) ng/mL when CsA is eliminated from the regimen. The studies showed that a concentration range of 15 to 30 ng/mL (measured by immunoassay) may be an adequate concentration range for patients whose CsA has been eliminated from the regimen. Higher doses of sirolimus were needed to maintain the concentration range.

Recommendations: Based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21-083 SE1-006 to fulfill section 320 and 201.5 of 21 CFR, the target trough concentration for sirolimus was achieved in the clinical studies. The proposed target trough concentration range for sirolimus (15 to 25 ng/mL via immunoassay after CsA

elimination) for the Rapamune Maintenance Regimen was empirically derived. The range is within the concentration range [redacted]

Recommended Phase IV Commitment: 1) The sponsor should develop an [redacted]

2/6/02

Kofi A. Kumi, Ph.D.
Reviewer
Clinical Pharmacology/Biopharm.
HFD-590 Section
DPE3/OCPB

Concurrence

Arzu Selen, Ph.D.
Deputy Director
DPE3/OCPB

2/8/2002

Summary of Clinical Pharmacology and Biopharmaceutics Findings

Sirolimus concentration-time data were obtained after administration of sirolimus oral solution and tablets to renal allograft recipients in one pivotal study and 3 supportive studies. Trough sirolimus concentration profiling was conducted in the studies in order to 1) characterize the pharmacokinetic behavior of sirolimus during concomitant administration with cyclosporine (CsA) and corticosteroids and after withdrawal of CsA from the regimen and 2) to determine the therapeutic window of sirolimus during a maintenance regimen after withdrawal of CsA. The pivotal study (study 310) and one supportive study (study 212) were reviewed in detail. Studies 207 and 210 were also reviewed. Among the studies (310, 212, 207, 210) submitted, 2 studies (310, 212) involved the elimination of CsA from 1 of the study treatment arms and 2 studies (207, 210) involved a comparison of sirolimus and CsA based triple immunosuppressive therapy. The dosing regimen in study 310 is similar to the proposed Rapamune maintenance regimen the sponsor is seeking approval. The dosing regimen for studies 310 and 212 are provided in the following table

Table 1

TABLE 3.1A. STUDY DESIGNS FOR SIROLIMUS AND CsA ADMINISTRATION DURING THE CONDUCT OF RMR TRIALS USING CONCENTRATION CONTROL

		Sirolimus				CsA			
Study	Group	Period	Loading Dose (mg)	Maintenance Dose (mg/day)	Target (ng/mL)	Period (month)	Dose (mg/day)	Target (ng/mL)	Complete CsA Withdrawal (month)
310	A and B[a]	Day 1	6			≤ 1	Individualized	200 to 400	-
		Day 2 to mo 3		2[b]	> 5	>1 to 3	Individualized	150 to 300	-
	A[a]	>3 to 36 mo	-	2[b]	> 5	>3 to 5.5	Individualized	150 to 250	-
		-	-	-	-	>5.5 to 36	Individualized	75 to 200	-
	B[a]	>3 to 12 mo	Individualized	Individualized	20 to 30	>3 to 5.5	Individualized	-	4 to 6
		>12 to 36 mo	Individualized	Individualized	15 to 25	-	-	-	-
212	A[a]	Day 1	6	-	-	≤ 1	Individualized	200 to 400	-
		Day 2 to 12 mo	-	2	-	>1 to 2	Individualized	200 to 350	-
		-	-	-	-	>2 to 3	Individualized	200 to 300	-
		-	-	-	-	>3 to 12	Individualized	150 to 250	-
	B[a]	Days 1 to 3	20	-	-	≤ 1	Individualized	100 to 175	-
		Days 4 to 9	10	-	-	>1 to 2	Individualized	100 to 150	-
		Day 11 to mo 12	Individualized	Individualized	10 to 20	>2 to 3	↓ 25%/wk	-	3

Abbreviations: CsA = cyclosporine; RMR = Rapamune Maintenance Regimen; mo = month.
a: Regimen also included corticosteroids.
b: The dose of sirolimus could have been increased up to 5 mg/day if the sirolimus trough was repeatedly < 5 ng/mL (sirolimus immunoassay [IMx]).

The dose algorithm used in sirolimus concentration-control trials was evaluated by estimating the percentages of patients with sirolimus concentrations below, within, and above the sirolimus target concentration range. The following table provides a summary of the descriptive statistics for the average percentages of patients with sirolimus concentrations below, within, and above the target ranges.

TABLE 4.1A. AVERAGE PERCENTAGES OF PATIENTS BELOW, WITHIN, AND ABOVE THE TARGET SIROLIMUS CONCENTRATIONS RANGES IN CONCENTRATION-CONTROL STUDIES DURING ≤ 1 YEAR AFTER TRANSPLANT

Study	Target Range (ng/mL)	Time Interval (months)	Visits	Average Percentages (%) ± SD (min, max) Below Range	Within Range	Above Range
207	10 to 20	3 to 12	11	5.73 ± 5.93 (0, 17)	72.6 ± 10.3 (55, 89)	16.7 ± 6.6 (5, 26)
210	10 to 20	>2 to 12	13	2.33 ± 2.89 (0, 8.3)	75.5 ± 10.2 (64, 93)	22.2 ± 9.8 (7.4, 36)
212	10 to 20	1 to 12	11	10.9 ± 4.9 (2.7, 22)	64.9 ± 5.2 (60, 75)	24.2 ± 6.7 (13, 32)
310	15 to 25	>3 to 12	11	29.3 ± 7.6 (20, 41)	61.5 ± 4.2 (54, 66)	9.2 ± 4.3 (2.6, 15)
All	-	-	46	11.6 ± 11.8 (0, 41)	68.9 ± 9.7 (54, 93)	18.3 ± 9.1 (2.6, 36)

Table 2 (above)

Among the 4 studies, 61.5% to 75.5% of patients had sirolimus concentrations within the target range, and 70.7% to 97.7% of patients had concentrations that were above the lower limit of the target concentration ranges.

The distribution of trough whole blood sirolimus concentration for concentration-controlled sirolimus administration is provided in the following figure

Based on trough concentration profiling, a concentration range of 15 to 25 ng/mL (immunoassay) is suggested for concentration-controlled sirolimus, when used without CsA. This concentration range is within the 10th and 90th percentile of sirolimus concentration observed in the clinical studies as shown below(Dotted lines = 10th and 90th percentile).

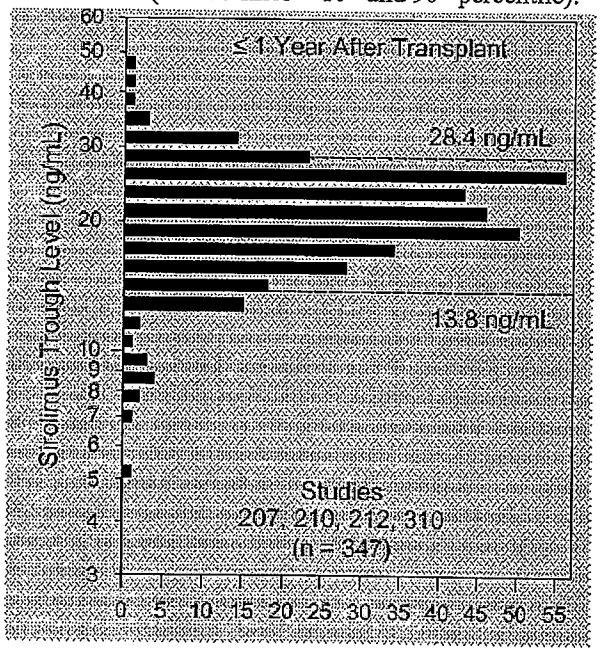


Fig 1

The sponsor reported that the proposed therapy offers comparable rates of acute rejection, graft survival, and patient survival while offering a statistically significant improvement in renal function. The sponsor reported that the data suggest sirolimus may allow for optimization of prophylactic immunosuppression by 1) reducing the incidence of acute rejection if used with CsA in the immediate postoperative period, and 2) sparing many patients the attendant toxicities of prolonged CsA exposure if CsA is subsequently eliminated from the therapeutic regimen.

Table of Contents

Question Based Review

What are the general attributes of Sirolimus?

Rapamune (sirolimus, Rapamycin) 1 mg/mL oral solution and 1 mg tablets were previously approved under NDA 21-083 and 21-110, respectively. Sirolimus is an immunosuppressive agent. It is a macrocyclic lactone produced by the fermentation of Streptomyces hygroscopicus. It is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone and acetonitrile.

Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-5) stimulation. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. This complex binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle.

In the clinical trials, efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death. Renal function was also evaluated. Biopsy proven acute rejection in the first 75 days post transplant was used in pharmacokinetic-pharmacodynamic evaluation while the patients were on triple therapy of sirolimus, CsA and corticosteroids. This analysis is similar to that submitted with the original application. This supplemental NDA for Rapamune maintenance regimen is for elimination of CsA after 2 –4 months of triple therapy. The data submitted did not allow evaluation of exposure-response analysis after the patients were randomized to CsA elimination arm of the therapy.

What analytical methods were used to determine sirolimus and CsA in blood or plasma?

Abbott immunoassay (IMx) testing system and chromatographic bioanalytical methods were used for the assay of whole blood sirolimus concentrations. Because of immunochemical cross-reactivity by metabolites, concentrations measured by IMx are higher than concentrations measured by chromatographic methods. The bias due to cross-reactivity has been shown to be approximately 25% for both the high performance liquid chromatography (HPLC)/tandem mass spectrophotometry (MS/MS) and HPLC with UV detection (HPLC/UV) methods. Therefore, for purposes of pharmacokinetic analysis, the following relationship has been used to convert measured concentrations by chromatographic methods to concentrations by IMx:

$$\text{IMx assay (ng/mL)} = 1.25 \bullet \text{chromatographic assay (ng/mL)}$$

Blood sirolimus was determined at local or central laboratories using a microparticulate enzyme system (IMx) through 31 December, 1999. The limit of quantitation (LOQ) is 1.5 ng/mL. The linear range was 3 – 30 ng/mL. The analytical method was changed to HPLC assay. The LOQs for the HPLC/MS/MS, HPLC/MS/MSII and HPLC/UV methods were 0.2 ng/mL, 1.0 ng/mL and 2.5 ng/mL, respectively. The linear ranges for HPLC/MS/MS, HPLC/MS/MSII and HPLC/UV were 0.2 – 100 ng/mL, 1 to 50 ng/mL and 2.5 – 50 ng/mL, respectively.

Whole blood CsA concentrations were determined by the investigator by monoclonal technique (TDX [Abbott Diagnostics, Abbott Park, IL, USA], CYCLOTrac SP (Incstar Corporation, Stillwater, MN, USA) or EMIT (Dade Behring Inc., Deerfield, IL, USA)]. All laboratories participated in the International Cyclosporine Proficiency Testing Scheme (Analytical Unit, Cardiological Sciences, St. George's Hospital Medical School, London, UK).

The analytical methods were validated and acceptable. These analytical methods have been used in other studies involving sirolimus and CsA. They were submitted and reviewed in NDA s 21-083 and 21-110.

The IMx assay is not currently available. Blood samples have to be shipped to specific laboratories for analysis and results reported to the clinician. The turn around time could be a rate-limiting step in the expeditious and timely application of TDM for sirolimus.

What were the sirolimus exposures in the two treatment regimens?

Time normalized average trough concentrations (Cmin,TN) and average doses (Dose,TN) were evaluated in these studies. Cmin,TN = AUC(0-t)/t and DoseTN = AUD(0-t)/t where AUC(0-t) is the area under trough concentration-time profile from the start of dose administration to time t. AUD(0-t) is the area under the dose curve from the start of dose administration up to time t. Cmin, TN was used as a method of estimating trough concentration in the original applications for sirolimus oral solution and tablets (NDAs 21-083 and 21-110). This method was preferred since estimating average concentrations this way permitted weighting of each trough concentration according to its time interval.

The means (10 th , 90 th percentiles) for average sirolimus doses (DoseTN) over days 136 to 385 for Groups A (nominally sirolimus 2 mg with CsA) and B (sirolimus concentration controlled without CsA) were 2.09 (1.50, 2.71) mg/day and 8.24 (3.80, 13.6) mg/day, respectively. The corresponding means (percentiles) for average trough whole blood sirolimus concentrations (Cmin,TN) over days 137 to 386 for Groups A and B were 10.8 (6.30, 15.8) ng/mL and 23.3 (16.9, 29.6) ng/mL, respectively.

The mean ± SE sirolimus doses for group A (nominally 2 mg/day sirolimus), group B (concentration-controlled sirolimus with CsA elimination), and the nonrandomized group over 385 days is provided in the table on the following page.

Mean doses for group A remained relatively constant over the 385-day period according to protocol design. Mean sirolimus doses for group B increased sharply beginning at approximately 3 months and appears to attain a plateau after approximately 5 months. The increases in dose for group B reflect changes that were required by the study protocol to achieve target trough sirolimus concentrations of 20 to 30 ng/mL during a period of declining CsA doses. ANOVA was used to compare only randomly assigned patients (group A and group B) over the interval of 136 to 385 days, which was the most appropriate comparative time period for the 2 groups. Significant differences in sirolimus DoseTN values between groups A and B were found with respect to treatment ($p = 0.001$). The significant difference with respect to treatment was expected because of the study design differences for groups A and B.

TABLE 10.1A. DAILY MEAN (± SEM) DOSES (mg/day) OF SIROLIMUS FOR PATIENTS IN ALL TREATMENT GROUPS: 12 MONTHS

	Nonrandomized (SRL + CSA)			Group A (SRL + CsA)			Group B (SRL)		
Time Slot	n	Mean ± SEM (mg/day)	Min – Max (mg/day)	n	Mean ± SEM (mg/day)	Min – Max (mg/day)	n	Mean ± SEM (mg/day)	Min – Max (mg/day)
Days 1-3	95	3.47 ± 0.055	2.00 - 6.00	215	3.49 ± 0.035	3.00 - 6.00	215	3.41 ± 0.030	1.67 - 7.00
Days 4-10	89	2.09 ± 0.063	1.17 - 5.00	215	2.08 ± 0.032	1.17 - 5.00	215	2.05 ± 0.030	1.29 - 5.00
Days 11-17	79	2.14 ± 0.104	1.00 - 7.14	213	2.09 ± 0.037	1.00 - 5.00	214	2.06 ± 0.033	1.00 - 5.00
Days 18-22	71	2.21 ± 0.145	1.00 - 10.00	213	2.10 ± 0.043	1.00 - 5.00	214	2.07 ± 0.036	1.00 - 5.00
Month 1	65	2.27 ± 0.136	1.00 - 7.20	215	2.12 ± 0.043	1.00 - 5.00	215	2.09 ± 0.041	1.00 - 5.00
Days 38-53	53	2.16 ± 0.161	1.00 - 8.75	215	2.17 ± 0.052	0.66 - 5.31	215	2.15 ± 0.051	1.00 - 6.00
Month 2	41	2.35 ± 0.298	1.00 - 13.33	215	2.14 ± 0.049	0.50 - 5.40	215	2.12 ± 0.041	1.00 - 6.00
Days 69-83	31	2.25 ± 0.229	1.00 - 8.00	215	2.11 ± 0.049	0.50 - 6.00	215	2.20 ± 0.052	1.00 - 7.75
Month 3	24	2.44 ± 0.284	1.00 - 8.00	215	2.12 ± 0.045	0.70 - 6.00	215	3.46 ± 0.120	1.00 - 10.00
Days 99-113	10	2.23 ± 0.260	1.00 - 4.00	214	2.14 ± 0.047	0.83 - 5.00	215	5.64 ± 0.222	1.07 - 24.40
Month 4	3	2.00 ± 0.000	2.00 - 2.00	213	2.11 ± 0.048	0.50 - 5.00	212	6.94 ± 0.291	1.00 - 38.75
Days 130-144	1	2.00	2.00 - 2.00	211	2.10 ± 0.047	0.77 - 5.00	209	7.60 ± 0.307	1.00 - 28.40
Month 5				209	2.10 ± 0.050	1.00 - 5.00	205	8.17 ± 0.316	1.00 - 25.00
Days 160-175				207	2.16 ± 0.055	1.00 - 5.00	200	8.45 ± 0.314	1.00 - 25.00
Month 6				205	2.17 ± 0.057	1.00 - 5.77	195	8.70 ± 0.308	1.05 - 25.00
Month 7				201	2.10 ± 0.052	1.00 - 6.00	189	8.58 ± 0.317	1.17 - 27.67
Month 8				197	2.08 ± 0.052	1.00 - 5.90	181	8.56 ± 0.332	2.18 - 35.00
Month 9				194	2.10 ± 0.056	1.00 - 7.00	175	8.31 ± 0.342	1.07 - 37.17
Month 10				191	2.05 ± 0.056	0.50 - 7.74	171	7.98 ± 0.307	1.55 - 32.74
Month 11				190	2.01 ± 0.060	0.50 - 9.57	168	7.81 ± 0.301	1.50 - 28.00
Month 12				185	2.03 ± 0.057	0.94 - 8.29	163	7.83 ± 0.316	1.00 - 30.00

Table 3 (above)

Figure 10.1A. Sirolimus Trough Levels (ng/mL, Immunoassay)

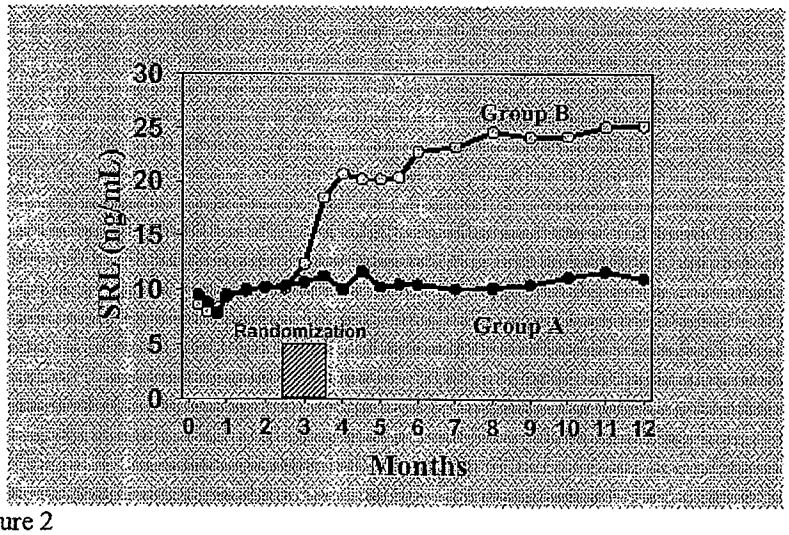


Figure 2

Similarly in supportive study (212), mean doses for group A remained approximately constant after day 7 over the 385-day period, while mean doses for group B declined initially before attaining plateau levels. The means (10 th , 90 th percentiles) for average sirolimus doses (DoseTN) over days 31 to 385 for Groups A (nominally sirolimus 2 mg with CsA) and B (sirolimus concentration controlled without CsA) were 1.89 (1.12, 2.0) mg/day and 6.14 (2.57, 9.78) mg/day, respectively. Consistently, sirolimus doses in the CsA elimination group were higher than those who were maintained on CsA.

In the pivotal study, the mean trough sirolimus concentrations for all groups were closely overlapped during the initial 3-month period before randomization (fig 2, previous page). The data show that the trough whole blood sirolimus concentrations for group A were generally at steady state over the 386-day time interval. Mean sirolimus trough concentrations for group B increased beginning at approximately 3 months and appears to stabilize within the target concentration range (20 to 30 ng/mL) after approximately 7 months.

Table 4

TABLE 11.1.4.2A. STATISTICAL SUMMARY FOR AVERAGE TROUGH WHOLE BLOOD SIROLIMUS CONCENTRATIONS ($C_{min,TN}$, ng/mL) OVER THE TIME-INTERVAL OF 137 TO 386 DAYS

Treatment	Characteristic	N	Actual ng/mL (%CV)[b,c]	Normalized[a] ng/mL (%CV)[b,c]
Group A (sirolimus 2 mg)	Black	3	9.72 (18/22)	9.59 (18/22)
	Non-black	201	10.8 (36/30)	11.1 (45/30)
	Male	137	10.6 (37/30)	11.1 (47/30)
	Female	67	11.0 (33/30)	11.2 (42/30)
	All	204	10.8 (36/30)	11.1 (45/30)
Group B (conc.-control)	Black	2	24.6 (10/23)	2.91 (14/23)
	Non-black	198	23.3 (22/31)	6.67 (45/31)
	Male	122	23.3 (21/30)	6.54 (46/30)
	Female	78	23.2 (23/34)	6.77 (45/11)
	All	200	23.3 (22/31)	6.63 (46/31)

Source of Variation	p-Values from ANOVA[d]	
Treatment	0.001	0.001
Sex	0.78	0.70
Treatment *Sex	0.67	0.89

a: Troughs normalized to a 2-mg dose
b: CV% = Intersubject/Intrasubject.
c: Intrasubject CV% taken from $Dose_{ave}$.
d: ANOVA is not shown for race due to the small number of black patients.

There was a significant difference in Cmin,TN with respect to treatment, but this difference was expected based on the protocol design. Patients in group B (concentration controlled) had concentrations that were approximately 2-fold greater than those for group A (sirolimus 2 mg/day).

In the supportive study, based on actual whole blood sirolimus trough concentrations (Cmin,TN), ANOVA by treatment showed significant differences between groups A and B over 32 to 386 days. The mean sirolimus Cmin,TN value in group B (concentration controlled sirolimus) was 2.2-fold greater than the mean Cmin,TN in group A (2 mg/day sirolimus). The targeted therapeutic concentration range was achieved for both studies.

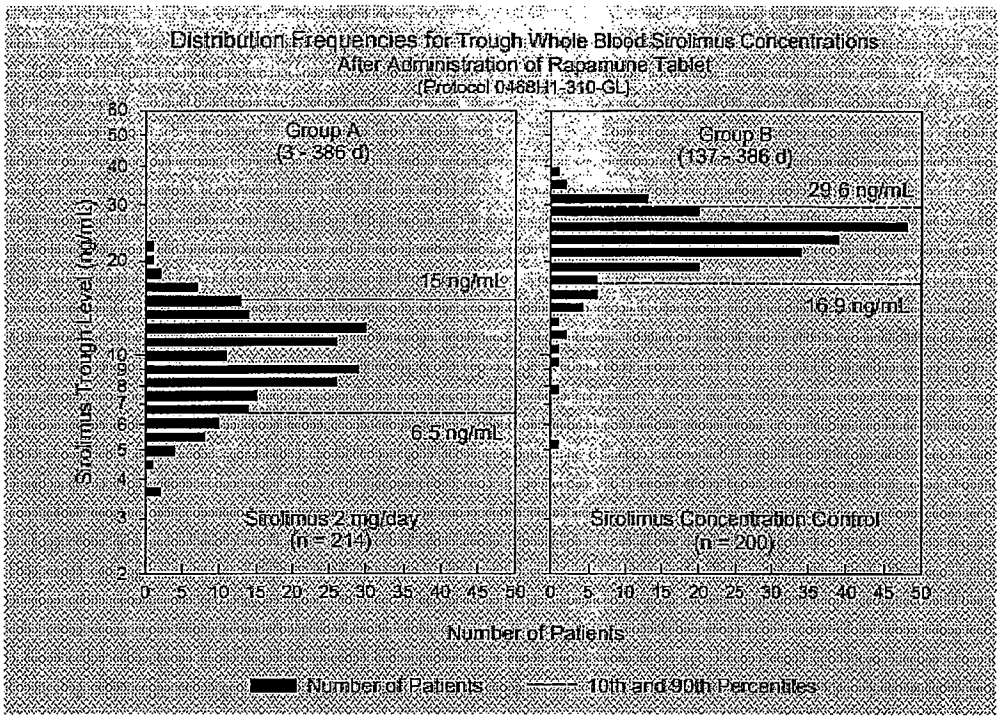

Distribution Frequencies for Trough Whole Blood Sirolimus Concentrations
After Administration of Rapamune Tablet
(Protocol 0468H1-310-GL)
Group A
(3 - 386 d)
Group B
(137 - 386 d)
29.6 ng/mL
16.9 ng/mL
15 ng/mL
6.5 ng/mL
Sirolimus Trough Level (ng/mL)
Sirolimus 2 mg/day
(n = 214)
Sirolimus Concentration Control
(n = 200)
Number of Patients
Number of Patients
10th and 90th Percentiles

Fig 3

The frequency distributions for trough whole blood sirolimus concentrations observed for group A (sirolimus 2 mg) and group B (concentration-controlled sirolimus) is provided in the above figure 3 (previous page). The data for group B showed that a concentration range of approximately 17 to 30 ng/mL sirolimus trough concentration was observed for most of the patients during a maintenance regimen without CsA. Similarly, the data for group A showed that a concentration range of approximately 6 to 15 ng/mL was observed for most of the patients during sirolimus dose-control regimen with concomitant CsA and corticosteroids. The sponsor reported that there was no statistically significant difference in biopsy proven rejection for patients in both groups. However, renal function at 12 month is reported to be significantly better in the CsA elimination group compared to those patients who were maintained on the regimen that included CsA. Therefore, the concentration range observed for the CsA eliminating group was therapeutically advantageous for these patients. The sponsor is recommending a concentration range of 15 to 25 ng/mL for treatment in patients who are maintained on sirolimus and corticosteroids without CsA.

What were CsA exposure in the two treatment groups?

The trough whole blood CsA concentrations for all groups declined in parallel up to approximately 3 months after transplantation based on protocol-designated dose reductions. Beyond 3 months, mean CsA troughs in group A approached near plateau levels; and in group B, mean CsA doses declined sharply and then dropped to near zero levels. The sharp decline for group B reflects the protocol-designated elimination of CsA from patients enrolled in this treatment group. CsA elimination was achieved in the treatment as mandated by the protocol.

The distribution profile for CsA shown in figure 4 illustrates successive declines in the CsA Cmin,TN distribution frequencies over time during concomitant administration with sirolimus tablet 2-mg/day. The mean (%CV) trough concentration for CsA in Group A for periods 2-31, 32-91, 92-386, 182-386 days were 288 (43) ng/mL, 233 (40) ng/mL, 154 (29) ng/mL and 147 (29) ng/mL, respectively. For group B, mean values for periods 2-31 and 32 –91 days were 284 (37) ng/mL and 228 (38) ng/mL.

The mean (%CV) CsA doses in Group A for periods 1-30, 31 – 90, 91 – 385, 185 – 385 days were 433 (32) mg, 308 (36) mg, 228 (34) mg and 218 (35) mg, respectively. For group B, the mean (%CV) CsA doses for periods 1 –30 and 31 – 90 days were 420 (31) and 298 (32) mg respectively. The overall decreases in CsA DoseTN during the intervals 31 to 90 days and 91 to 385 days were –28.9% and –49.7%, respectively, for group A and –29.0% and –96.2%, respectively, for group B

Table 5

MEAN WHOLE BLOOD TROUGH CYCLOSPORINE CONCENTRATIONS ($C_{min,TN}$, ng/mL) OVER SEQUENTIAL TIME INTERVALS UP TO 386 DAYS

			2-31 days			32-91 days			92-386 days[a]			182-386 days	
			Actual	Normalized		Actual	Normalized		Actual	Normalized		Actual	Normalized
Treatment	Characteristic	n	ng/mL (%CV)[b,c]	ng/mL (%CV)	n	ng/mL (%CV)[b,c]	ng/mL (%CV)	n	ng/mL (%CV)[b,c]	ng/mL (%CV)	n	ng/mL (%CV)[b,c]	ng/mL (%CV)
Group A	Black	4	208 (52/53)	168 (25/-)	4	223 (10/18)	202 (21/-)	4	142 (12/39)	241 (23/-)	3	130 (10/30)	212 (20/-)
	Non-Black	200	290 (43/34)	213 (47/-)	169	233 (40/27)	250 (43/-)	207	154 (29/31)	221 (37/-)	192	148 (29/28)	220 (45/-)
	Male	138	283 (47/34)	198 (48/-)	115	232 (36/27)	232 (38/-)	141	153 (27/33)	208 (36/-)	131	144 (26/29)	207 (44/-)
	Female	66	300 (34/36)	243 (43/-)	58	233 (47/27)	282 (46/-)	70	156 (32/29)	246 (35/-)	64	154 (34/26)	247 (37/-)
	All	204	288 (43/35)	212 (47/-)	173	233 (40/27)	249 (43/-)	211	154 (29/32)	221 (37/-)	195	147 (29/28)	220 (42/-)
Group B	Black	2	82 (71/36)	96 (38/-)	2	159 (1/38)	150 (1/-)	NA	NA	NA	1	0 (-/-)	0 (-/-)
	Non-Black	197	286 (36/33)	215 (41/-)	166	229 (38/25)	246 (47/-)	NA	NA	NA	173	3.3 (-/-)	6.8 (-/-)
	Male	124	277 (38/33)	191 (42/-)	103	230 (38/25)	223 (45/-)	NA	NA	NA	105	5.5 (-/-)	9.6 (-/-)
	Female	75	296 (37/33)	252 (36/-)	65	225 (38/25)	280 (46/-)	NA	NA	NA	69	0 (-/-)	2.5 (-/-)
	All	199	284 (37/33)	214 (41/-)	168	228 (38/25)	245 (47/-)	NA	NA	NA	174	3.3 (-/-)	6.8 (-/-)

	p-Values from ANOVA[d,e]	
Source of Variation	Actual	Normalized
Treatment	0.54	0.98
Sex	0.094	0.001
Treatment *Sex	0.90	0.75
Interval	0.001	0.001
Interval*Sex	0.054	0.37

a: NA = not applicable since concentrations were decreasing rapidly during part of the interval.
b: CV% = Intersubject/Intrasubject.
c: Intrasubject CV% taken from Dose[illegible] (see ST11-18 and ST12-19).
d: A comparison of intervals 2-31 vs 32-91 only.
e: ANOVA for analysis by race not shown due to the small number of black patients.

MEAN CYCLOSPORINE DOSES ($Dose_{TN}$, mg/day) OVER SEQUENTIAL TIME INTERVALS UP TO 385 DAYS

Treatment	Characteristic	1-30 days n	1-30 days mg (%CV)[b,c]	31-90 days n	31-90 days mg (%CV)[b,c]	91-385 days[a] n	91-385 days mg (%CV)[b,c]	181-385 days n	181-385 days mg (%CV)[b,c]
Group A (2 mg)	Black	4	351 (31/26)	4	338 (15/10)	4	185 (26/36)	3	188 (19/10)
	Non-black	210	435 (32/22)	210	307 (36/12)	210	228 (34/13)	200	218 (35/9)
	Male	142	451 (32/21)	142	328 (34/12)	142	239 (33/14)	136	230 (34/9)
	Female	72	397 (30/25)	72	268 (36/12)	72	204 (35/11)	67	193 (34/10)
	All	214	433 (32/22)	214	308 (36/12)	214	228 (34/13)	203	218 (35/9)
Group B (conc.-control)	Black	2	241 (39/31)	2	318 (2/8)	NA	NA	1	0 (-/-)
	Non-black	212	422 (30/21)	212	298 (32/12)	NA	NA	192	16 (-/-)
	Male	132	457 (29/20)	132	325 (31/13)	NA	NA	118	20 (-/-)
	Female	82	360 (27/23)	82	255 (26/11)	NA	NA	75	10 (-/-)
	All	214	420 (31/21)	214	298 (32/12)	NA	NA	193	16 (-/-)

Source of Variation	p-value from ANOVA[d,e]
Treatment	0.008
Sex	0.001
Treatment*Sex	0.21
Interval	0.001
Interval*Sex	0.21

a: NA = not applicable since doses were decreasing rapidly during part of the interval.
b: CV% = Intersubject/Intrasubject.
c: Intrasubject CV% taken from $Dose_{ss}$ [illegible]
d: A comparison of intervals 1-30 vs 31-90.
e: The analysis by race is not shown due to the small n-value in black patients.

Table 6

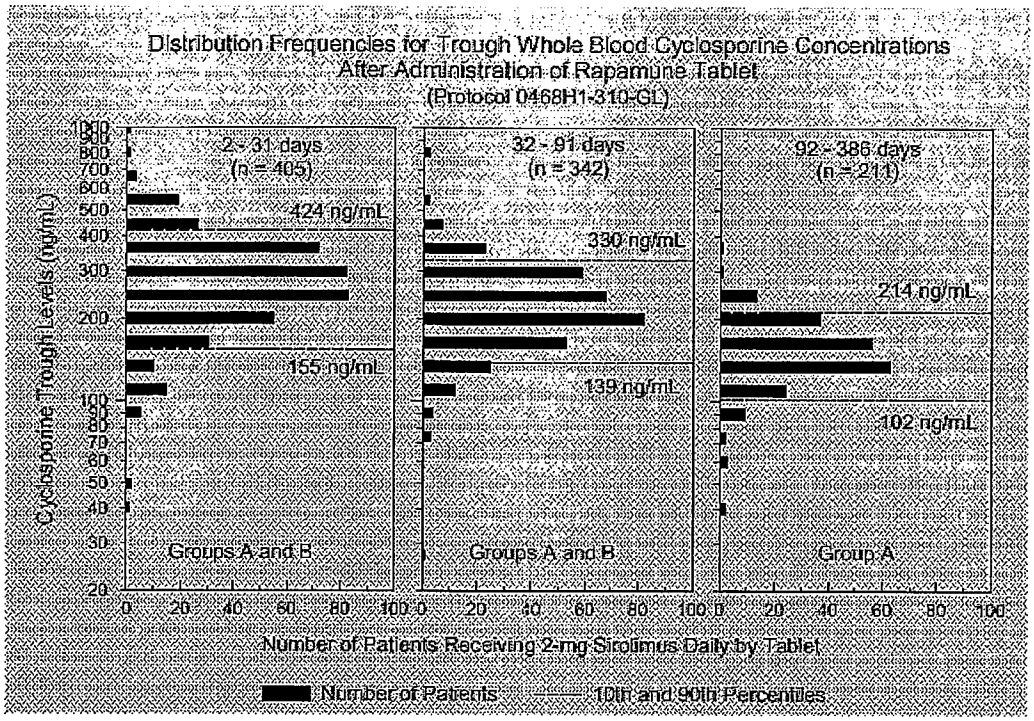

Distribution Frequencies for Trough Whole Blood Cyclosporine Concentrations
After Administration of Rapamune Tablet
(Protocol 0468H1-310-GL)
2 - 31 days
(n = 405)
424 ng/mL
155 ng/mL
Groups A and B
32 - 91 days
(n = 342)
330 ng/mL
139 ng/mL
Groups A and B
92 - 386 days
(n = 211)
214 ng/mL
102 ng/mL
Group A
Cyclosporine Trough Levels (ng/mL)
Number of Patients Receiving 2-mg Sirolimus Daily by Tablet
Number of Patients
10th and 90th Percentiles

Figure 4

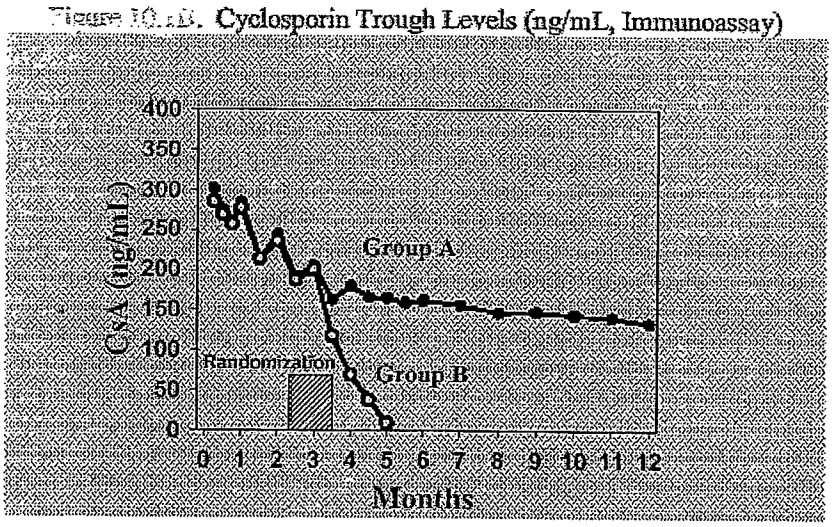


Figure 10.1.B. Cyclosporin Trough Levels (ng/mL, Immunoassay)
400
350
300
250
200
150
100
50
0
Group A
Randomization
Group B
0 1 2 3 4 5 6 7 8 9 10 11 12
Months

Figure 5

Is there any concentration-effect relationship?

The sponsor demonstrated via logistic regression analysis that biopsy proven acute rejection within the first 75 days may be related to sirolimus and CsA concentrations. The probability of acute rejection at fixed CsA concentration decreased with an increase in sirolimus concentration.

The influence of sirolimus and CsA concentrations on acute rejection, confirmed by biopsy, after adjusting for necessary explanatory variables was examined by logistic regression analyses. The independent variables in the model were (a) sirolimus concentration, (b) CsA concentration, (c) race (black and nonblack), (d) sex (female and male), (e) recipient age, (f) donor age, (g) HLA mismatch, and (h) ischemia time.

A multivariate logistic regression model was tested that included terms for dichotomized sirolimus concentrations, dichotomized CsA concentration, sex, recipient, HLA mismatch, and age*HLA mismatch. The cutoff points used for sirolimus and CsA were 5 ng/mL and 150 ng/mL, respectively. These cutoff points were chosen for 3 reasons: 1) 5 ng/mL for sirolimus and 150 ng/mL for CsA are the lower recommended target levels for these drugs during the first 3 months before randomization. 2) They were relatively close to the first quartile of each variable in the logistic model. 3) These concentrations are close to the 10 th percentile in the observed concentrations in the study and correspond to potential lower limits of target ranges when the drugs are used together.

The analysis showed statistical significance for dichotomized sirolimus ($p = 0.0001$), dichotomized CsA ($p = 0.0452$), sex ($p = 0.0244$), age ($p = 0.0128$), age*HLA mismatch ($p = 0.0430$) but not for HLA mismatch ($p = 0.123$).

After exclusion of the HLA mismatch term, all explanatory variables retained statistical significance ($p = 0.05$) except dichotomized CsA concentrations ($p = 0.0512$). Based on the odds ratio in the final model, the probability of acute rejection was approximately 4.7 times more likely when sirolimus concentrations were below 5 ng/mL with CsA concentration greater than 150 ng/mL and 2.2 times more likely when sirolimus concentrations were greater than 5 ng/mL with CsA concentration below 150 ng/mL

Table 7

TABLE 14.2.1.13A. FINAL MULTIVARIATE LOGISTIC REGRESSION MODEL WITH SIROLIMUS AND CYCLOSPORINE DICHOTOMIZED[a]

Variable	Slope Estimate	Wald Chi-Square p-Value	Odds Ratio Estimate
Intercept	-1.0826	0.0630	-
Sirolimus (dichotomized)	1.5523	0.0001	4.722
CsA (dichotomized)	0.7799	0.0512	2.181
Sex	-0.6847	0.0221	0.504
Age	-0.0358	0.0185	0.965
Age•HLA mismatch	0.00493	0.0424	1.005

a: Sirolimus and cyclosporine were dichotomized at 5 ng/mL and 150 ng/mL, respectively (the value of the variable equals 1 when the concentration is less than the cutoff value and 0 otherwise).

Table 8

SUPPORTIVE TABLE ST11-23. DESCRIPTIVE STATISTICS OF DRUG EXPOSURES AND DEMOGRAPHIC VARIABLES IN RENAL ALLOGRA PATIENTS RECEIVING DAILY ORAL DOSES OF SIROLIMUS AS RAPAMUNE TABLETS, CYCLOSPORINE AND CORTICOSTEROIDS

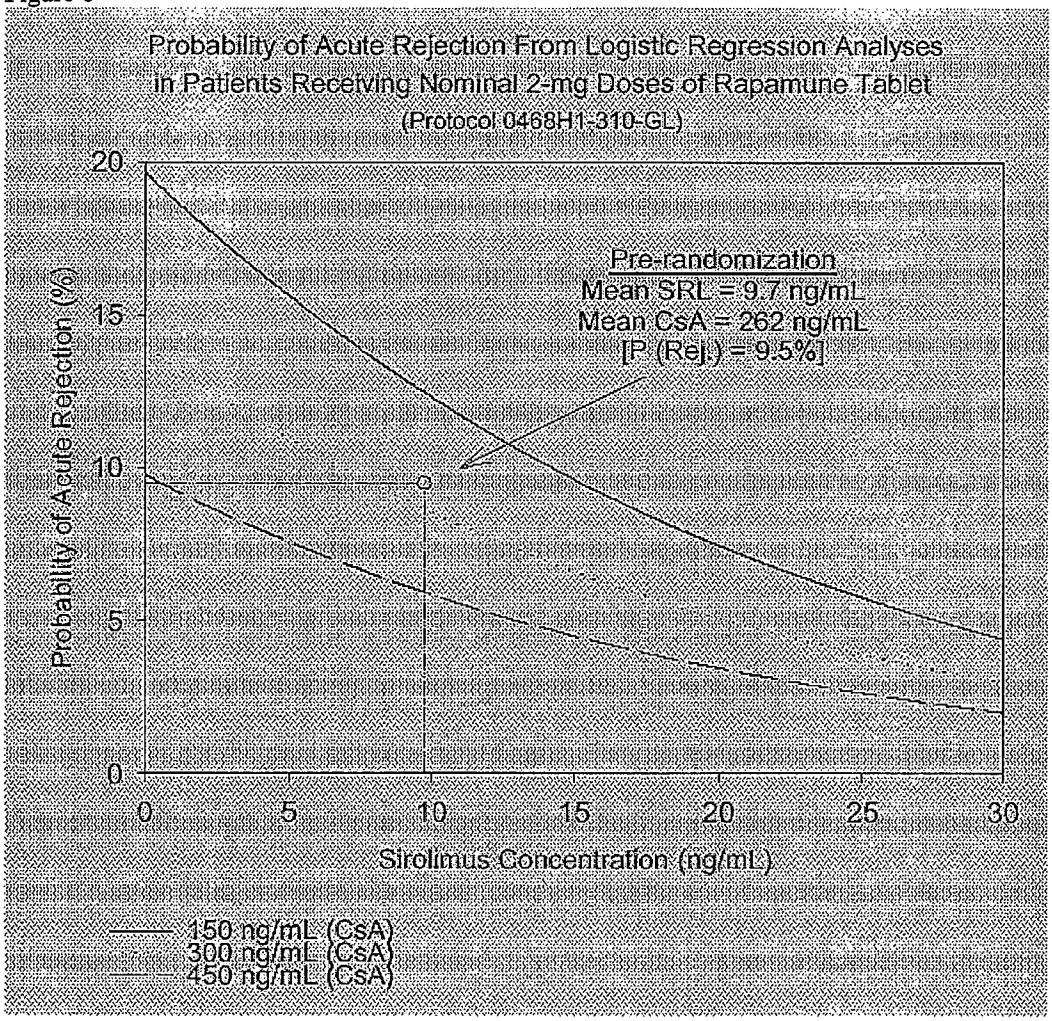
PROTOCOL 0468H1-310-GL

VARIABLE	ASSIGNED GROUP	*** PATIENTS WITH NO REJECTIONS *** N	MEAN	S.D.	CV %	***** PATIENTS WITH REJECTIONS **** N	MEAN	S.D.	CV %	T-TEST P-VALUE
AVERAGE SIROLIMUS TROUGH	GROUP A	199	9.77	3.57	36.5	16	8.58	4.31	50.2	0.2078
	GROUP B	195	9.77	3.21	32.8	17	8.91	4.88	54.7	0.3170
	NON-RAND.	66	10.39	5.39	51.8	23	8.64	4.82	55.8	0.1719
	OVERALL	460	9.86	3.74	37.9	56	8.70	4.62	53.0	0.0347
AVERAGE CSA TROUGH	GROUP A	199	267.70	89.53	33.4	16	208.28	113.68	54.6	0.0131
	GROUP B	195	265.82	95.48	35.9	17	243.72	95.92	39.4	0.3614
	NON-RAND.	66	257.43	158.26	61.5	23	249.85	121.85	48.8	0.8349
	OVERALL	460	265.43	104.26	39.3	56	236.11	111.63	47.3	0.0492
RECIPIENT AGE	GROUP A	199	46.04	11.71	25.4	16	42.94	10.57	24.6	0.3067
	GROUP B	195	45.17	12.94	28.7	17	38.82	14.14	36.4	0.0556
	NON-RAND.	66	50.35	13.56	26.9	23	45.26	12.80	28.3	0.1197
	OVERALL	460	46.29	12.61	27.2	56	42.64	12.71	29.8	0.0418
HLA MISMATCH	GROUP A	199	2.92	1.36	46.4	16	3.06	1.34	43.8	0.6957
	GROUP B	195	2.97	1.22	41.0	17	2.76	1.64	59.3	0.5201
	NON-RAND.	66	2.53	1.38	54.7	23	3.57	1.62	45.4	0.0040
	OVERALL	460	2.89	1.31	45.3	56	3.18	1.56	49.1	0.1242
ISCHEMIA TIME	GROUP A	197	17.48	9.15	52.3	16	22.28	10.30	46.2	0.0472
	GROUP B	192	16.25	8.85	54.5	16	17.43	8.31	47.7	0.6076
	NON-RAND.	65	17.85	7.03	39.4	23	17.33	10.53	60.8	0.7899
	OVERALL	454	17.01	8.76	51.5	55	18.79	9.94	52.9	0.1608
DONOR AGE	GROUP A	199	44.13	14.93	33.8	16	42.56	15.79	37.1	0.6887
	GROUP B	195	41.39	15.94	38.5	17	45.35	16.35	36.1	0.3276
	NON-RAND.	65	48.38	16.93	35.0	23	46.13	16.88	36.6	0.5843
	OVERALL	459	43.57	15.80	36.3	56	44.88	16.19	36.1	0.5597

GROUP A = 2 MG/DAY SIROLIMUS AFTER 3 MONTHS
GROUP B = CONCENTRATION CONTROL SIROLIMUS AFTER 3 MONTHS

A reduced model was developed for purposes of graphical illustration. The reduced model excluded sex because it is a discontinuous variable. Age was fixed to a median value of 47 years, HLA was fixed at a median value of 3, and CsA concentrations were fixed at concentrations of 150, 300, and 450 ng/mL to generate 3 plots. The results of the simulations for the probability of acute rejection (expressed as a percentage) vs sirolimus concentration are shown in the following figure.

Figure 6



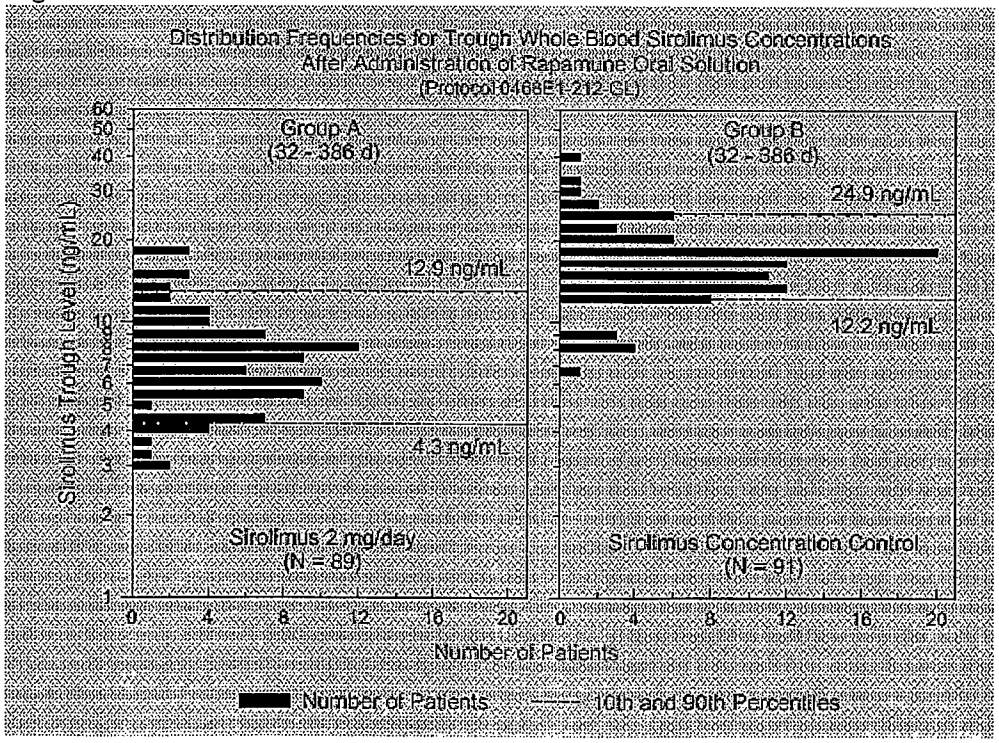
The addition of sirolimus to a CsA regimen decreases the probability of acute rejection rate at all CsA concentrations. Based on the model excluding sex, it can be estimated that probability of acute rejection during the first 2 months would be approximately 16% when whole blood concentrations of sirolimus and CsA are as low as 5 ng/mL and 150 ng/mL, respectively. Similar analysis were conducted in NDA 21-083 and 21-110. The results of that analysis also suggested that the probability of biopsy proven acute rejection decreased with increase in sirolimus concentration at fixed CsA concentration.

What were the basis for selection of the target trough concentration range for the pivotal phase III study (Study 310)?

The sponsor conducted pilot studies in which they reported that when patient sirolimus trough concentrations were maintained within 10 – 20 ng/mL, acute rejections were similar to immunosuppressive regimens including cyclosporine. Exploratory exposure-response analysis conducted in the original New Drug Application (NDA 21083) demonstrated that at fixed cyclosporine concentration, increasing sirolimus concentration decreased the probability of acute rejection.

The following figure shows the frequency distributions for trough whole blood sirolimus (Cmin,TN) observed for groups A (sirolimus 2 mg) and B (concentration controlled sirolimus as measured by IMx assay in the supportive clinical study (212). It is noted that the 10th and 90th percentiles for group B of 12.2 and 24.9 ng/mL, respectively, were slightly above the protocol-designated target concentration range limits of 10 and 20 ng/mL..

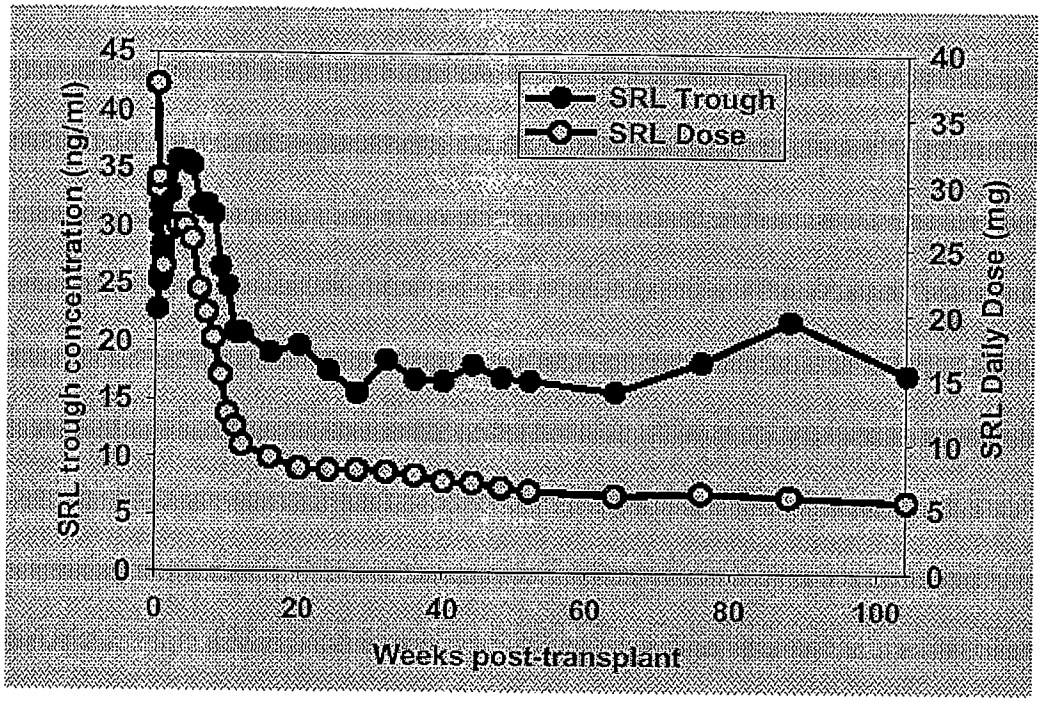
Figure 7



In a small pilot study (210) in which sirolimus and CsA based immunosuppressive triple therapy were compared, the protocol specified that sirolimus target trough levels of 30 ng/mL for the first 2 months and 15 ng/mL thereafter were to be obtained for patients given sirolimus,. For patients on CSA based therapy, trough concentration of 200 to 400 ng/mL for 2 months followed by 100

to 200 ng/mL from week 8 onward. Sirolimus and CsA target trough levels were achieved. Each treatment arm contained mycophenolate mofetil and corticosteroids. In a similar study in which azathioprine was administered instead of mycophenolate mofetil, target trough concentrations were achieved. The sponsor reported that these small pilot studies suggested sirolimus based therapies without CsA were efficacious in prophylaxis against organ rejection in renal transplant patients. The trough concentration observed in these studies aided in the selection of the target trough sirolimus concentration for the two CsA elimination studies.

Fig 8: Mean Sirolimus Dose and Trough concentration obtained in study 210



In NDA 21083, administration of sirolimus with CsA resulted in increase in sirolimus concentrations. However, sirolimus had no effect on CsA concentrations when they were administered together. It is anticipated that sirolimus concentration will decrease if administered without CsA. Higher doses of sirolimus may be needed to maintain similar trough concentrations and immunosuppressive effect.

Are there any ethnic and/or gender differences in the RMR?

There were too few blacks in the study to perform statistical analysis to determine whether there was significant differences in the doses and trough concentrations administered to black patients. No gender difference in dose or trough sirolimus concentration was observed in the pivotal study.

Based on protocol design and for exploratory purposes, average doses were summarized by intervals of 2 to 90, 91 to 135, 91 to 385, and 136 to 385 days for all groups. However, the ANOVA was used to compare only randomly assigned patients (group A on CsA and group B without CsA) over the interval of 136 to 385 days, which was the most appropriate comparative time period for the 2 groups since CsA by that time has been eliminated from the regimen for group B patients. Significant differences in sirolimus DoseTN values between groups A and B

were not found for sex ($p = 0.49$) and treatment*sex ($p = 0.48$) over the sirolimus concentration-control interval of 136 to 385 days. Similarly, significant differences in gender were not found in trough concentrations.

Table 9

STATISTICAL SUMMARY FOR AVERAGE TROUGH WHOLE BLOOD SIROLIMUS CONCENTRATIONS ($C_{min,TN}$, ng/mL) OVER THE TIME-INTERVAL OF 137 TO 386 DAYS

Treatment	Characteristic	N	Actual ng/mL (%CV)[b,c]	Normalized[a] ng/mL (%CV)[b,c]
Group A (sirolimus 2 mg)	Black	3	9.72 (18/22)	9.59 (18/22)
	Non-black	201	10.8 (36/30)	11.1 (45/30)
	Male	137	10.6 (37/30)	11.1 (47/30)
	Female	67	11.0 (33/30)	11.2 (42/30)
	All	204	10.8 (36/30)	11.1 (45/30)
Group B (conc.-control)	Black	2	24.6 (10/23)	2.91 (14/23)
	Non-black	198	23.3 (22/31)	6.67 (45/31)
	Male	122	23.3 (21/30)	6.54 (46/30)
	Female	78	23.2 (23/34)	6.77 (45/11)
	All	200	23.3 (22/31)	6.63 (46/31)
	Source of Variation		p-Values from ANOVA[d]	
	Treatment		0.001	0.001
	Sex		0.78	0.70
	Treatment *Sex		0.67	0.89

a: Troughs normalized to a 2-mg dose
b: CV% = Intersubject/Intrasubject.
c: Intrasubject CV% taken from $Dose_{ave}$ [illegible]
d: ANOVA is not shown for race due to the small number of black patients.

The results of ANOVA, comparing CsA DoseTN values over intervals 1-30 days and 31-90 days, showed significant differences with respect to treatment ($p = 0.009$), sex ($p = 0.001$), and time interval ($p = 0.001$) but not for treatment*sex ($p = 0.21$) or interval •sex ($p = 0.20$). Mean CsA DoseTN were larger in males than in females for each treatment group.

What was the dosing algorithm used to adjust sirolimus dosing during the pivotal study?

Dose adjustment from randomization through month 12 based on sirolimus whole-blood trough level

Sirolimus trough level Action

< 20 ng/mL (Imx). Administer the Loading Dose and the New Maintenance Dose together on the first day then the New Maintenance Dose daily thereafter

20-30ng/mL (Imx): No adjustment needed

>30 ng/mL (Imx): Calculate a New Maintenance Dose and administer daily

Sirolimus Loading Dose = 3 x (New Maintenance Dose - Current Maintenance Dose)
Desired Maintenance Dose = Current Maintenance Dose x (25ng/mL (using IMx assay)) divided by current sirolimus trough level)

The current sirolimus trough level may be the average of more than one value.
The prescribed dose should be determined from the calculated dose.
The maximum daily dose should not exceed 40 mg. If the total dose (Loading Dose + Maintenance Dose) exceeds 40 mg, then the loading dose should be administered over two days.

If the sirolimus blood level is below the limit of quantification (1.5 ng/mL IMx), then assume the current trough concentration is 1.5 ng/mL (IMx) for the purpose of calculating the initial loading and maintenance doses.

Overall Conclusions

The sponsor demonstrated in the pivotal and supportive pilot study that therapeutic drug monitoring is feasible for sirolimus. The studies suggested that a concentration range of 15 to 30 ng/mL (measured by immunoassay) may be an adequate sirolimus concentration range to maintain in patients whose CsA has been eliminated from a regimen that includes sirolimus and corticosteroids. It was reported by the sponsor that slightly higher (about 6%) biopsy proven rejections were observed after CsA withdrawal and significantly improved renal function at 12 months was observed in the patients who were maintained on the regimen that eliminated CsA compared to those that were maintained on CsA. Therefore, the observed concentrations can provide adequate exposures in these patients.

An approved commercial immunoassay is not currently widely and easily available to measure sirolimus concentration. Sirolimus was measured in specific sites at specific locations in the clinical studies. The lack of an easily and widely available assay to determine sirolimus concentration in TDM may be a rate limiting step in the successful application of TDM. It is recommended that the sponsor provide specific plans to develop such an assay. This will make sirolimus therapeutic drug monitoring easier and practical.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kofi Kumi
5/15/02 03:18:33 PM
BIOPHARMACEUTICS

You signed hard copy on 2/8/02

Arzu Selen
5/16/02 08:56:57 PM
BIOPHARMACEUTICS

Bacho, Matthew A

From: Carreras, Jose A
Sent: Wednesday, June 13, 2001 1:49 PM
To: Bacho, Matthew A
Subject: RE: Efficacy supplements for NDAs 21-083 and 21-110 (Rapamune)

No questions, Thanks,

Jose

-----Original Message-----
From: Bacho, Matthew A
Sent: Wednesday, June 13, 2001 1:42 PM
To: Carreras, Jose A
Cc: Cavaille Coll, Marc W; Tiernan, Rosemary; Dixon, Cheryl A; Higgins, Karen M
Subject: Efficacy supplements for NDAs 21-083 and 21-110 (Rapamune)

Jose,

We do not intend to request any inspections for NDA 21-083/SE1-006 and NDA 21-110/SE1-004 because many of the clinical sites were already inspected as part of the original applications in 1999 and 2000 for Rapamune Oral Solution and Tablets, respectively. If you have any questions, please feel free to contact me.

Thanks,
Matt

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-083 / S-006
21-110 / S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Rapamune® (sirolimus)
sNDA No. 21-083

Item 16 **Debarment Certification**

Wyeth-Ayerst hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetics Act in connection with this supplement to application No. 21-083 for Rapamune®.

Signed: _____

Maureen D. Skowronek
Assistant Vice President
Worldwide Regulatory Affairs

Patent / Exclusivity Information

1)	Active ingredient(s)	Sirolimus
2)	Strength(s)	1 mg
3)	Trade Name	Rapamune®
4)	Dosage Form (Route of Administration)	Tablet in bottles of 100 tablets Redipak® of 100 tablets
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	21-110
7)	Approval Date	TBD
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA.
9)	Applicable patent numbers and expiration date of each	U.S. Patent 5,100,899, Normal Expiration Date: June 6, 2009 U.S. Patent 5,212,155, Normal Expiration Date: May 18, 2010 U.S. Patent 5,308,847, Normal Expiration Date: May 3, 2011 U.S. Patent 5,403,833, Normal Expiration Date: April 4, 2012 U.S. Patent 5,989,591, Normal Expiration Date: March 11, 2018

Patent / Exclusivity Information

1)	Active ingredient(s)	Sirolimus
2)	Strength(s)	2 mg
3)	Trade Name	Rapamune®
4)	Dosage Form (Route of Administration)	Tablet in bottles of 100 tablets Redipak® of 100 tablets
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	21-110
7)	Approval Date	TBD
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA.
9)	Applicable patent numbers and expiration date of each	U.S. Patent 5,100,899, Normal Expiration Date: June 6, 2009 U.S. Patent 5,212,155, Normal Expiration Date: May 18, 2010 U.S. Patent 5,308,847, Normal Expiration Date: May 3, 2011 U.S. Patent 5,403,833, Normal Expiration Date: April 4, 2012 U.S. Patent 5,989,591, Normal Expiration Date: March 11, 2018

Patent/Exclusivity Information

1)	Active ingredient(s)	Sirolimus
2)	Strength(s)	1 mg per 1 ml
3)	Trade Name	Rapamune®
4)	Dosage form (Route of Administration)	Oral liquid concentrate in bottles (60 ml and 150 ml) and foil pouches (1 ml, 2 ml and 5 ml)
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	21-083
7)	Approval Date	TBD
8)	Exclusivity – Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA.
9)	Applicable patent numbers and expiration date of each	U.S. Patent 5,100,899, Normal Expiration Date: June 6, 2009 U.S. Patent 5,212,155, Normal Expiration Date: May 18, 2010 U.S. Patent 5,308,847, Normal Expiration Date: May 3, 2011 U.S. Patent 5,403,833, Normal Expiration Date: April 4, 2012 U.S. Patent 5,536,729, Normal Expiration Date: September 30, 2013

TIME SENSITIVE PATENT INFORMATION PURSUANT TO 21 C.F.R. 314.53
for NDA 21-110

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	RAPAMUNE"
Active Ingredient(s):	sirolimus (rapamycin)
Strength(s):	1 mg
Dosage Form:	Tablets, Oral
Approval Date:	to be determined

A. Information for each individual patent:

US Patent Number: 5,100,899
Expiration Date: June 6, 2009
Type of Patent: Method of Use - inhibiting transplant rejection using rapamycin.
Patent Owner: Sir Roy Calne
US Agent: American Home Products Corp., parent company of the Applicant, is the exclusive licensee under the patent.

US Patent Number: 5212,155
Expiration Date: May 18, 2010
Type of Patent: Method of Use - inhibiting transplant rejection using rapamycin in combination with cyclosporin.
Patent Owner: Sir Roy Calne
US Agent: American Home Products Corp., parent company of the Applicant, is the exclusive licensee under the patent.

US Patent Number: 5308,847
Expiration Date: May 3, 2011
Type of Patent: Method of Use - inhibiting transplant rejection using rapamycin in combination with azathioprine.
Patent Owner: Sir Roy Calne
US Agent: American Home Products Corp., parent company of the Applicant, is the exclusive licensee under the patent.

US Patent Number: 5,403,833
Expiration Date: April 4, 2012
Type of Patent: Method of Use - inhibiting transplant rejection using rapamycin in combination with a cotticosteroid.
Patent Owner: Sir Roy Calne
US Agent: American Home Products Corp., parent company of the Applicant, is the exclusive licensee under the patent.

TIME SENSITIVE PATENT INFORMATION PURSUANT TO 21 C.F.R. 314.53
for NDA 21-110

A. Information for each individual patent (continued):

US Patent Number: 5,989,591
Expiration Date: March 11, 2018
Type of Patent: Drug Product (Composition/Formulation) - RAPAMUNE" oral tablet formulation
Patent Owner: American Home Products Corp., parent company of the Applicant, is the owner of the patent.

B. Declaration statement for listed patents which have Compostion/Formulation or Method of Use claims:

The undersigned declares that the above stated US Patent No. 5,100,899 covers the method of use of RAPAMUNE". This product is the subject of this application for which approval is being sought.

The undersigned declares that the above stated US Patent No. 5,212,155 covers the method of use of RAPAMUNE®. This product is the subject of this application for which approval is being sought.

The undersigned declares that the above stated US Patent No. 5,308,847 covers the method of use of RAPAMUNE". This product is the subject of this application for which approval is being sought.

The undersigned declares that the above stated US Patent No. 5,403,833 covers the method of use of RAPAMUNE". This product is the subject of this application for which approval is being sought.

The undersigned declares that the above stated US Patent No. 5,989,591 covers the formulation of RAPAMUNE". This product is the subject of this application for which approval is being sought.

WYETH-AYERST LABORATORIES

By: _____
Arnold S. Milowsky, Ph.D.
Patent Counsel .
Date: 3 /15/01

EXCLUSIVITY SUMMARY for NDA # 21-083 & 21-110 SUPPL # 006/004

Trade Name Rapamune® Generic Name sirolimus

Applicant Name Wyeth Pharmaceuticals HFD- 590

Approval Date April 11, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Wyeth Pharmaceuticals, Inc. requested three (3) years of exclusivity.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-083 Rapamune Oral Solution

NDA # 21-110 Rapamune Tablets

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 212

Investigation #2, Study # 310

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # 212

Investigation #_2_, Study # 310

Investigation #___, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 39,160 YES /_X_/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /_X_/ Explain: Study was conducted outside the United States.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 (N/A)

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2 (N/A)

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title: _____

_____ _____

Signature of Office of Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Matthew Bacho
4/14/03 03:46:26 PM
NDAs 21-083/S-006 & 21-110/S-004

Steven Gitterman
4/15/03 01:24:29 PM

T03-25
April 10, 2003

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA APPROVES NEW RAPAMUNE LABELING LIKELY TO IMPROVE TRANSPLANTED KIDNEY FUNCTIONING

The Food and Drug Administration (FDA) today announced the approval of revised labeling for Rapamune(sirolimus) that will allow new kidney transplant patients at low to moderate immunologic risk of organ rejection to stop taking cyclosporine 2 to 4 months after transplantation. By substituting higher levels of Rapamune for cyclosporine, it is hoped that kidney function will improve.

Today's action is the first approval of a cyclosporine-sparing regimen for new kidney transplant patients. Currently, all kidney transplant patients are treated with a combination of medications -- typically three or more immunosuppressant drugs -- to prevent organ rejection.

More than one-half of all new kidney transplant patients could potentially benefit from this newly approved regimen. In the year 2000 alone there were 14,427 kidney

-More-

transplants in the United States, according to the U.S. Renal Data System, a project of the National Institute of Diabetes & Digestive & Kidney Diseases at the National Institutes of Health.

The combined use of Rapamune and cyclosporine is necessary but may carry long-term risks to the transplanted kidney function. The ability to take kidney transplant patients off cyclosporine 2-4 months after transplantation, without increased risk of organ rejection, is therefore likely to be associated with improved kidney function.

FDA based its decision on the results of a randomized, multi-center controlled clinical trial that enrolled 525 patients. This study assessed the safety and efficacy of Rapamune as a maintenance regimen, comparing patients who were administered Rapamune, cyclosporine and corticosteroids continuously with patients who received the same standardized therapy for the first 3 months after transplantation followed by the withdrawal of cyclosporine. At 12, 24 and 36 months after transplantation, organ and patient survival were similar for both groups.

Clinical research is currently underway to assess the safety and efficacy of cyclosporine withdrawal in new

kidney transplant patients at high-risk of organ rejection, as well as kidney transplant patients who have been taking a combination of immunosuppressive medications for more than 4 months. Therefore, cyclosporine withdrawal and concentration controlled Rapamune use is not being recommended at this time in these additional patient populations.

Wyeth Pharmaceuticals Inc., of Philadelphia, Pa., is the sponsor of the approved New Drug Application (NDA) for Rapamune.

####

146 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Administrative-*_____

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-083 and 21-110 Supplement Type (e.g. SE5): SE1 Supplement Number: 006 and 004

Stamp Date: April 9 and 18, 2001/October 15, 2002 (Class 2 Resubmission) Action Date: April 11, 2003

HFD 590 Trade and generic names/dosage form: Rapamune® (sirolimus) Oral Solution and Tablets

Applicant: Wyeth Pharmaceuticals Therapeutic Class: Immunomodulator

Indication(s) previously approved: Prophylaxis of acute rejection in renal transplant recipients

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: In patients at low to moderate immunologic risk, cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune® dose should be increased to reach recommended blood concentrations.

Is there a full waiver for this indication (check one)?

☒ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☒ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☒ Too few children with disease to study
☐ There are safety concerns
☒ Other: Wyeth has a Written Request for pediatric studies in renal transplantation.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-083 and 21-110
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Matthew Bacho
4/18/03 05:38:03 PM
NDAs 21-083/S-006 & 21-110/S-004

NDA 21-083/S-006
NDA 21-110/S-004

Dear Mr. Brenner:

Please refer to your supplemental NDAs 21-083/S-006 and 21-110/S-004, which were submitted on April 6 and 16, 2001, for Rapamune® Oral Solution and Tablets, respectively. Our reviewing statistician would like to request the following information:

Please provide the following analysis datasets for studies 310 and 212. The datasets should be set up as one row per patient and include the following variables:

Efficacy Dataset

- Patient ID
- Investigator ID
- Country
- Treatment group
- Donor Source (living/cadaver)
- VFE population (yes/no, Study 212)
- Day of randomization (all day values are relative to time of study enrollment)
- Day of start of cyclosporine withdrawal (where applicable)
- On therapy at 12 months (yes/no)

- Graft loss at 12 months (yes/no, 1/0)
- Reason for graft loss (pure, death with functioning graft, etc.)
- Day of graft loss
- Period of graft loss (pre-randomization, post-randomization, follow-up)

- Acute rejection at 12 months (yes/no, 1/0)
- Day of rejection
- Period of rejection
- Grade of rejection

- Death at 12 months (yes/no, 1/0)
- Day of death
- Period of death

- Discontinuation from study at 12 months (yes/no, 1/0)
- Day of discontinuation
- Period of discontinuation

Lab Dataset (GFR and Serum Creatinine)

- Patient ID
- Investigator ID
- Country
- Treatment group
- On therapy at 12 months (yes/no)
- For Nankivell GFR (Z909)
- Baseline value
- Last value prior to cyclosporine withdrawal or randomization for study 310
- Month 12 value (if no month 12 result give last available result and flag as to time period for value reported)
- For Serum Creatinine (C785)
- Baseline value
- Last value prior to cyclosporine withdrawal or randomization for study 310

Month 12 value (if no month 12 result give last available result and flag as to time period for value reported)

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Matthew Bacho
12/21/01 05:20:23 PM
CSO
NDAs 21-083/S-006 and 21-110/S-004

NDA 21-083/S-006
NDA 21-110/S-004

Dear Mr. Brenner:

Please refer to NDAs 21-083/S-006 and 21-110/S-004, which were submitted on April 6 and 16, 2001, for Rapamune® Oral Solution and Tablets, respectively. Our reviewing clinical pharmacologist would like to request the following information:

1. Please provide, in a tabular format, the data used in the concentration-effect (PK-PD) analysis for the first 75 days. The following information is required: subject identification, gender, race, weight, sirolimus concentration, CsA concentration, and clinical outcome [e.g., BPR/acute rejection, and safety (e.g., renal function and lipid levels)]. For gender and race, please use numbers to indicate the gender or race (e.g., female = 1 and male = 2). This is the desired format:

Subject ID	Gender	Race	Sirolimus Conc.	CsA Conc.	Clinical Outcomes (Efficacy)	Clinical Outcome (Safety)	HLA

2. If available, please provide a tabular format for the data for PK-PD analysis for 75 – 360 days. Please indicate the time of randomization for these patients. The following information is required: subject identification, gender, race, weight, randomization, time of randomization, sirolimus concentration, cyclosporine concentration, and clinical outcome [e.g., BPR/acute rejection and safety (e.g., creatinine clearance and lipid levels)]. For gender and race, please use numbers to indicate the gender or race (e.g., female = 1 and male = 2). This is the desired tabular format:

Subject ID	Gender	Race	Randomization		Srl. Conc.	CsA Conc.	Clinical Outcomes (Efficacy)	Clinical Outcome (Safety)	HLA
			Time	Trt.					

3. We recommend that you analyze the data for the 75 – 360 days using both logistic regression and classification and regression analysis. We are particular interested in concentration-effect (PK-PD) analysis after randomization.

We are providing the above information via telephone facsimile for your convenience. Please

feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Matthew Bacho
12/13/01 05:35:12 PM
CSO
NDAs 21-083/S-006 and 21-110/S-004

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-083/S-006
NDA 21-110/S-004
IND 39,160

Wyeth-Ayerst Research
Attention: Randy Brenner
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Brenner:

Reference is made to your correspondence to IND 39,160 dated March 20, 2001; to your supplemental New Drug Application (NDA 21-083/S-006) dated April 6, 2001; and to your supplemental New Drug Application (NDA 21-110/S-004) dated April 16, 2001, requesting a deferral for pediatric studies under 21 CFR 314.55(b).

We have reviewed the information you have submitted and agree that a deferral is justified for Rapamune® (sirolimus) Oral Solution, 1 mg/mL and Tablets, 1 mg, for the prophylaxis of organ rejection in pediatric patients receiving renal transplants, when used initially in a regimen with cyclosporine and corticosteroids and considering cyclosporine withdrawal 2 to 4 months after transplantation.

The agency has not made a determination if a health benefit would be gained by studying Rapamune® in pediatric patients for this proposed indication. FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations because pediatric studies should be delayed until additional safety or effectiveness data have been collected and reviewed. FDA will inform you on or before April 9, 2004, whether pediatric studies are required under the rule. If FDA determines at that time that pediatric studies are necessary, FDA will also set a specified time at which you must submit the required assessments.

If you have any questions, call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Mark Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Mark Goldberger
6/21/01 01:27:56 PM
NDA 21-083/S-006, NDA 21-110/S-004

implementation of the Administrative Simplification provisions (Social Security Act, title XI, part C, 42 U.S.C. 1320d to 1320d–8) of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Pub. L. No. 104–191.

Its Subcommittee on Privacy and Confidentiality monitors developments in health information privacy and confidentiality on behalf of the full Committee and makes recommendations to the full Committee so that it can advise the Secretary on implementation of the health information privacy provisions of HIPAA.

Purpose: This meeting of the Subcommittee on Privacy and Confidentiality will receive information on the implementation of the regulation "Standards for Privacy of Individually Identifiable Health Information" (45 CFR parts 160 and 164), promulgated under the Health Insurance Portability and Accountability Act of 1996.

The regulation and further information about it can be found on the Web site of the Office for Civil Rights, at *http://www.hhs.gov/ocr/hipaa/*. The regulation has been in effect since April 14, 2001. Most entities covered by the regulation must come into compliance by April 14, 2003, and many are beginning the process of implementing it.

The first day of the meeting will be conducted as a hearing, in which the Subcommittee will gather detailed information about implementation of the regulation's provisions for use and disclosure of health information for marketing and fundraising. The Subcommittee will invite specific representatives of affected groups, in order to obtain information about practical issues in implementation of the regulation with respect to these uses and disclosures of information, and to obtain suggestions about possible solutions for such issues.

The format will include one or more invited panels on these issues and time for questions and discussion. The Subcommittee will ask the invited witnesses for focused, detailed analyses and description, with examples, of the effect the regulation is expected to have, on individuals and on entities subject to the regulation, with respect to these matters, based on early implementation efforts and preliminary assessments of impact.

The second day of the meeting will consist of Subcommittee discussion of the testimony it has heard and deliberations about possible recommendations to the Secretary.

In addition to the panels that will be invited to address these issues, members of the public who would like to make a brief (3 minutes or less) oral comment on one or more of the specified issues during the hearing will be placed on the agenda as time permits. To be included on the agenda, please contact Marietta Squire (301) 458–4524, by E-mail at *mrawlinson@cdc.gov*, or postal address at NCHS, Presidential Building, Room 1100, 6525 Belcrest Road, Hyattsville, Maryland 20782 by January 17, 2002.

Persons wishing to submit written testimony only (which should not exceed five double-spaced typewritten pages) should endeavor to submit it by that date. Unfilled slots for oral testimony will also be filled on the day of the meeting as time permits. Please consult Ms. Squire for further information about these arrangements.

Additional information about the hearing will be provided on the NCVHS Web site at *http://www.ncvhs.hhs.gov* shortly before the hearing date.

Contact Person for More Information: Information about the content of the hearing and matters to be considered may be obtained from John P. Fanning, Lead Staff Persons for the NCVHS Subcommittee on Privacy and Confidentiality, Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, 440D Humphrey Building, 200 Independence Avenue SW., Washington DC 20201, telephone (202) 690–5896, E-mail *jfanning@osaspe.dhhs.gov*. or from Marjorie S. Greenberg, Executive Secretary, NCVHS, NCHS, CDC, Room 1100, Presidential Building, 6525 Belcrest Road, Hyattsville, Maryland 20782, telephone (301) 458–4245. Information about the committee, including summaries of past meetings and a roster of committee members, is available on the Committee's Web site at *http://www.ncvhs.hhs.gov*.

Dated: December 20, 2001.

James Scanlon,

Director, Division of Data Policy, Office of the Assistant Secretary for, Planning and Evaluation.

[FR Doc. 01–32198 Filed 12–31–01; 8:45 am]

BILLING CODE 4151–05–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Immunosuppressive Drugs Subcommittee of the Antiviral Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Immunosuppressive Drugs Subcommittee of the Antiviral Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on January 24, 2002, from 8:30 a.m. to 5 p.m.

Location: Holiday Inn, The Ballrooms, Two Montgomery Village Ave., Gaithersburg, MD.

Contact: Tara P. Turner, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane (for express delivery 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301–827–7001, e-mail: TurnerT@cder.fda.gov, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12531. Please call the Information Line for up-to-date information on this meeting.

Agenda: The subcommittee will discuss new drug applications (NDAs) 21–083/SE1–006 and 21–110/SE1–004, RAPAMUNE (sirolimus) oral solution and tablets, Wyeth-Ayerst Research, approved for prophylaxis of organ rejection in patients receiving renal transplants. As stated in the approved labeling, it is recommended that RAPAMUNE be used in a regimen with cyclosporine and corticosteroids. The discussion is for the proposed elimination of cyclosporine from the immunosuppressive regimen 2 to 4 months after transplantation under certain conditions.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the subcommittee. Written submissions may be made to the contact person by January 16, 2002. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before January 16, 2002, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: December 19, 2001.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 01–32175 Filed 12–31–01; 8:45 am]

BILLING CODE 4160–01–S

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC)
IMMUNOSUPPRESSIVE DRUGS SUBCOMMITTEE MEETING

AGENDA
January 24, 2002
Gaithersburg Holiday Inn
Two Montgomery Village Avenue
Gaithersburg, MD 20879

NDA 21-083 Rapamune® (sirolimus) Oral Solution – Cyclosporine Withdrawal Maintenance Regimen

8:30 a.m.	Call to Order and Opening Remarks	Janet A. Englund, M.D. Subcommittee Chair
	Introduction of Subcommittee	
	Conflict of Interest Statement	Tara P. Turner, Pharm. D. Executive Secretary, AVAC
8:40 a.m.	**FDA Introductory Remarks**	Renata Albrecht, M.D. Acting Director Division of Special Pathogen and Immunologic Drug Products, FDA
8:45 a.m.	**Sponsor Presentation**	Wyeth-Ayerst Research
	Introduction	Randall B. Brenner, M.S. Senior Manager Worldwide Regulatory Affairs
	Overview Design of Clinical Studies Efficacy Review Safety Review	John F. Neylan, M.D. Vice President Transplantation Immunology, Clinical Research and Development
	Pharmacokinetics Concentration-Controlled Trials Therapeutic Drug Monitoring	James Zimmerman, Ph.D. Senior Director Clinical Pharmacokinetics, Clinical Research and Development
	Concluding Remarks	John F. Neylan, M.D.
10:45 a.m.	Break	

11:00 a.m.	**FDA Presentation**	Rosemary Tiernan, M.D., M.P.H. Medical Officer Division of Special Pathogen and Immunologic Drug Products, FDA
12:00 p.m.	Lunch	
1:00 p.m.	Open Public Hearing	
		Alan Wilkinson, M.D., F.R.C.P. Director, Kidney and Pancreas Transplantation Professor of Medicine UCLA
2:00 p.m.	Charge to the Subcommittee	Renata Albrecht, M.D.
2:10 p.m.	Subcommittee Discussion and Vote	
5:00 p.m.	Adjourn	

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC)
IMMUNOSUPPRESSIVE DRUGS SUBCOMMITTEE MEETING

QUESTIONS FOR THE SUBCOMMITTEE
January 24, 2002
Gaithersburg Holiday Inn
Two Montgomery Village Avenue
Gaithersburg, MD 20879

1.) Do the data presented support the effectiveness and safety of cyclosporine withdrawal and concentration controlled sirolimus 2 to 4 months after kidney transplantation, in patients treated initially with a regimen of sirolimus, cyclosporine and corticosteroids?

a.) If the answer is yes, should this consideration be restricted to a particular subpopulation? Conversely, is there a particular subpopulation for which cyclosporine withdrawal should not be considered?

b.) If the answer is no, what additional information would be needed to support such a maintenance regimen?

2.) What additional Phase 4 studies would you recommend?

3.) Do you have any comments or recommendations regarding study design and/or endpoints for controlled clinical trials intended to support the safety and efficacy of maintenance immunosuppressive regimens in renal transplantation?