

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021083

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Drug Evaluation IV/ Division of Special Pathogens and Immunologic Drug Products

DATE: August 31, 1999

TO: Mark J. Goldberger, M.D., Ph.D.
Division Director, HFD-590

FROM: Marc W. Cavallé-Coll, M.D., Ph.D.
Medical Officer Medical Team Leader, HFD-590 **IS** 8/3/99

SUBJECT: NDA 21-083, for Rapamune® (sirolimus) Oral Solution for the prophylaxis of organ rejection in allogeneic renal transplantation.

The major issues of this NDA have been thoroughly discussed in the pre-clinical, statistical and clinical reviews. I concur with the consensus of the reviewers that NDA 21-083, for Rapamune® (sirolimus) Oral Solution, should be approved for the indication of prophylaxis of organ rejection in patients receiving allogeneic renal transplants, to be used concomitantly with cyclosporine and corticosteroids. This memorandum will briefly comment on a few areas that have been discussed at some length during the review process.

The clinical development of Rapamune® was a global project involving clinical centers in the US, Canada, Europe and Australia. To date, a Centralized Application for authorization to market Rapamune® in the 15 countries of the European Union has been filed, as well as national applications in Switzerland, Norway, Turkey, and Canada. Final actions on these applications are still pending. The US regulatory action would represent the first approval for this new molecular entity in the world.

The original NDA was submitted to the FDA on December 15, 1998, and was given a priority drug classification based on its potential to meet a need for immunosuppressive agents in renal transplantation with novel mechanisms of action and non-overlapping adverse effects. During FDA's review of the NDA, the applicant discovered a programming error, which influenced the efficacy analyses. In particular, some episodes of biopsy-proven acute rejection were not properly identified in the electronic database. At a meeting on May 7, 1999, the applicant agreed to submit a revised Application Summary, a revised Integrated Summary of Efficacy, and amendments to the study reports which would include the suggested re-analysis of the primary and secondary endpoints the pivotal Phase 3 studies 301 and 302. By mutual agreement the inclusive primary analysis was based on a broader definition of any biopsy-confirmed acute rejection and included verified updated 6-month efficacy outcome data. The revised materials along with updated electronic data sets were submitted to the NDA on June 1, 1999. The need for submission of such a major clinical information amendment and a complete reanalysis by FDA, lead to a 90-day extension of the priority review timeline.

Rapamune® (sirolimus) is a novel immunosuppressive agent that acts by a mechanism that is non-redundant with those of other immunosuppressants approved for the prophylaxis of organ rejection in renal transplantation. Sirolimus, a macrocyclic lactone produced by *Streptomyces hygroscopicus*, binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. Unlike tacrolimus, which also binds to FKBP-12, 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 regulatory kinase involved in the pathway activated by antigen and cytokine (Interleukins 2, 4 and 15) stimulation. This inhibition suppresses cytokine-driven T-lymphocyte proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle.

Rapamune® is intended to be used with cyclosporine and corticosteroids. Sandimmune® (cyclosporine capsules and oral solution USP) and Neoral® (cyclosporine capsules and oral solution [MODIFIED]) were the cyclosporine formulations used in Phase 2 and Phase 3, respectively. Cyclosporine itself has an effect on the metabolism and pharmacokinetics of sirolimus. In the presence of cyclosporine, sirolimus C_{max} and AUC are increased. This interaction is formulation dependent when cyclosporine and Rapamune® are administered orally simultaneously. When coadministered with Sandimmune®, sirolimus trough concentrations (which correlate with AUC and C_{max}) are increased by approximately 75%. When coadministered with Neoral® sirolimus AUC is increased by approximately 220%. When Rapamune is administered orally 4 hours after Neoral® the increase in bioavailability is approximately 80%. In order to reproduce in Phase 3 the sirolimus doses evaluated in Phase 2 (1mg and 3 mg per meter square of body surface area) fixed doses of Rapamune®, 2mg and 5 mg, administered orally four hours after Neoral®, were used. It is proposed that components of the Neoral® formulation that enhance absorption of cyclosporine may also enhance the absorption of sirolimus, when Rapamune® is administered simultaneously, but not when Rapamune® is administered 4 hours later. Although it is recommended that Rapamune® be taken 4 hours after Neoral®, occasional lapses in compliance with this recommendation are unlikely to affect sirolimus blood levels, because of the long terminal half-life of this drug.

The safety and efficacy of Rapamune® is supported by two adequate well controlled studies, study 301 and study 302, which compared two doses of sirolimus, 2 mg per day and 5 mg per day, with azathioprine or placebo controls. Both studies were randomized, double blind and well conducted. The co-primary endpoints were efficacy failure, defined as an episode of biopsy-proven rejection, graft loss or death at six months, and 12-month patient and graft survival. The double blind design minimized an important potential source of bias in the assessment of episodes of acute rejection. There was also complete assessment of patient and graft survival at one year. Patient and graft survival, at 12 months, were similar across treatment groups. Although efficacy failure at six months was decreased with sirolimus 2 mg per day compared to azathioprine or placebo controls, this finding was not consistent across all groups of interest. In particular, in study 301, which was prospectively stratified by race within center, efficacy failure was similar for sirolimus 2 mg per day and lower for sirolimus 5 mg per day compared to azathioprine control in black patients. In study 302, which was not prospectively stratified by

race efficacy failure was similar for both sirolimus doses compared to placebo in black patients. Additional phase 4 investigations are needed to evaluate the optimal sirolimus dose and regimen in black patients.

Although there was a decrease in rate of episodes of biopsy proven rejection in patients treated with sirolimus compared to azathioprine or placebo controls, this was not associated with a detectable decrease in rates of complications associated with the additional immunosuppression used to treat such episodes. Nor were decreased rates of efficacy failure at six months in sirolimus treated patients associated with improved graft function at 12 months. Mean glomerular filtration rates (GFR) at one year post transplant were calculated using the Nankivell equation for all subjects in studies 301 and 302 who had serum creatinine measured at 12 months. In both studies, mean GFR, at 12 months, were lower in patients treated with cyclosporine and sirolimus compared to those treated with cyclosporine and the respective azathioprine or placebo control. This is contrary to what would have been expected, based on the differences in rates of acute rejection. However, within each treatment group in studies 301 and 302, mean GFR at 12 months post transplant was lower in patients who experienced at least one episode of acute rejection compared to those who did not.

Because cyclosporine dosing and whole blood trough concentrations were similar across treatment groups in these double blind studies, these differences in GFR could not be explained by differences in exposure to cyclosporine nephrotoxicity. However, it should be noted that mean cyclosporine trough levels remained at or above the upper limit of the prospectively defined target concentration ranges in both phase 3 studies. This is higher than what would be expected in clinical practice, and may reflect concern over possible insufficient immunosuppression in these double blind studies. More judicious monitoring and adjustment of cyclosporine dosing might spare some loss of renal function at 12 months. Overall, it is not possible to evaluate the relative contribution of potential drug toxicity and/or rejection to the observed differences in GFR at 12 months. The clinical importance of lower GFR at 12 months in the sirolimus treatment groups remains uncertain and will require additional evaluation and long-term follow-up of these patients during phase 4.

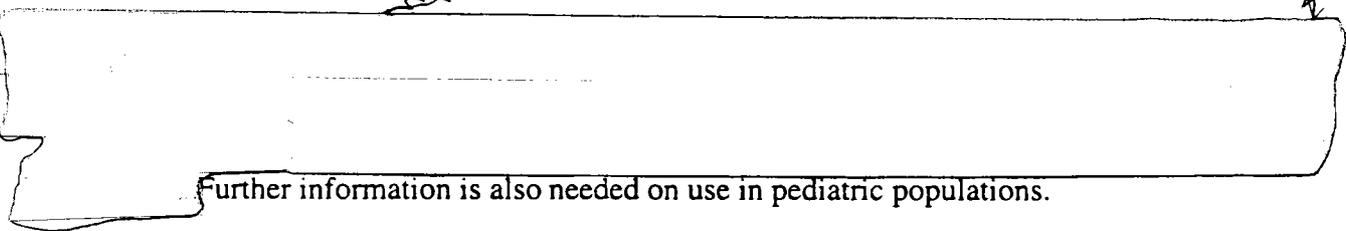
Although there is no preclinical information in the application which suggests that sirolimus is intrinsically nephrotoxic, the potential for sirolimus to increase the nephrotoxicity of concomitantly administered cyclosporine has not been adequately evaluated in non-clinical studies. The applicant has agreed to include such studies in their future plans for post-phase 3 investigations.

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 shown to be safe and effective, no efficacy advantage over the 2 mg dose could be established for renal transplant patients. In addition, patients receiving 2 mg of sirolimus per day demonstrated an overall better safety profile than did patients receiving 5 mg of sirolimus per day. Notable dose-dependent adverse events associated with the use of sirolimus include hyperlipemia, hypercholesterolemia, leukopenia and thrombocytopenia. Indeed, new-onset

hypercholesterolemia, that required treatment, developed in a significant proportion of patients treated with sirolimus. Although no excess in cardiovascular adverse events were detected in 12 months of follow-up of patients treated with sirolimus in the phase 3 studies, there is insufficient follow-up, to date, to evaluate the long term consequences of this type of toxicity. Cardiovascular disease is a leading cause of death in renal transplant patients beyond one year post-transplantation.



A meeting of the Subcommittee for Immunosuppressants of FDA's Antiviral Drug Products Advisory Committee was held on July 27, 1999. At that meeting the subcommittee agreed that sirolimus was safe and effective for the prevention of acute rejection, in patients receiving allogeneic renal transplants at a recommended daily dose of 2mg. The subcommittee also agreed that an alternate dose might be needed for specific populations. However, the information presented in Studies 301 and 302 did not support the sponsor's recommendation of a 5mg daily dose for high-risk patients. The majority of the subcommittee did recommend the inclusion of the 5mg data in the package insert.



Further information is also needed on use in pediatric populations.

**APPEARS THIS WAY
ON ORIGINAL**

Medical Officer's Review

NDA 21,083
M.O. Review #1
Submitted: December 15, 1998
Review completed: September 15, 1999

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

Chemical name: Rapamycin
(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentacontine-1,5,11,28,29(4H,6H,31H)-pentone

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

Pharmacologic Category : Immunosuppressant

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

Dosage Form(s) and Route(s) of Administration: 2mg/day and 5mg/day
oral solution (1 mg/ml)

NDA Drug Classification: 1-P

Related Reviews: Statistics dated August 20, 1999
Biopharmaceutics dated August 11, 1999
Pharmacology-Toxicology dated August 20, 1999
Immunology dated July 26, 1999
Chemistry dated August 30, 1999

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3. Material Reviewed

Volumes dated 12/15/98: 317,323,329,330 (including the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) submitted to FDA), the 3 month Safety Update submitted on 3/15/99 and the electronic submission "ERS" which includes "clinical section 8" and the case report forms(CRF) and the case report tabulations (CRT). Additional materials were reviewed and included the following jackets labeled "Response to FDA for information" and dated: January 14, 1999, March 17, 1999, April 1, 1999, April 12, 1999, May 13, 1999, May 21, 1999, May 28, 1999, Revised ISE dated June 1, 1999*, June 14, 1999, June 18, 1999, June 25, 1999, June 29, 1999, July 13, 1999, Summary of Advisory Committee Presentation July 27, 1999.

- * On April 14, 1999, Wyeth-Ayerst notified the Division of a programming error in the SAS program that was used to create the efficacy analysis data-sets. This error caused an under-reporting of biopsy-confirmed rejections. When the efficacy analysis data-sets were created, the acute rejections for investigators with alphanumeric identification numbers were not included. On May 7, 1999 a meeting was held to discuss the re-analysis of the efficacy data relative to pivotal Rapamune® studies 301 and 302. During the May 7th meeting, the Division suggested additional analyses which expanded the treatment window for acute rejection, a component of the composite primary efficacy endpoint.
- This was called the "inclusive analysis" and it permitted 24 patients who had biopsies positive for acute rejection to be represented after being excluded from the prospective primary analysis because treatment for acute rejection was not initiated within 48 hours of the biopsy procedure (Please refer to the Revised ISE dated June 1, 1999).

- Based on discussions between the FDA and Wyeth at the May 7, 1999 meeting, the NDA 21,083 submission was considered a major clinical amendment, a 3 month extension was added to the original PDUFA goal date of June 15, 1999 and the new PDUFA goal date was set at September 15, 1999.

4. Chemistry/Manufacturing Controls

Please refer to the Chemistry review dated August 30, 1999

Sirolimus is poorly soluble in water. Each mL of Rapamune® Oral Solution contains 1 mg sirolimus; inactive ingredients are Phosal 50 PG® (phosphatidylcholine, propylene glycol, monodiglycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and Polysorbate 80, NF. Rapamune® Oral Solution contains 1.5% to 2.5% ethanol. The amounts of ethanol that would be present in daily doses of Rapamune® are negligible. This formulation forms a dispersion when mixed with water. The inactive ingredients present in concomitantly administered cyclosporine formulations may affect the dispersion and absorption of sirolimus when administered simultaneously (see Human Pharmacology).

The proposed formulation is expected to have a shelf life of 2 years when refrigerated and protected from light. An important stability consideration is that a degradation product, seco-rapamune, resulting from the opening of the ring structure, may form if the product is left at room temperature for a prolonged period of time. Thus, it is recommended that Rapamune® Oral Solution bottles and pouches be stored protected from light and refrigerated at 2°C to 8°C (36°F to 46°F). Once a bottle is opened, the contents should be used within one month. It is recognized that these requirements may present a potential challenge to compliance in patients who may not have continuous access to refrigeration, while traveling for example. Because the formation of the degradant is a slow process, it is acceptable to allow the patient to store both the pouches and the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., several days, but not longer than 30 days).

Reviewer's note: This requirement to keep the Rapamune® oral solution refrigerated may contribute to problems with patient compliance.

Although it is believed that certain amounts of seco-rapamune were present in formulations used in pre-clinical pharmacology and toxicology studies, as well as clinical studies in humans, the individual immunosuppressant activity and potential toxicity of seco-rapamune is still unknown and should be evaluated in phase IV studies (See Phase IV Commitments dated August 24, 1999).

The reviewing chemist and pharmacologist-toxicologist have requested that the Applicant qualify the degradation product WAY-126792 (seco-rapamune) in a 3 month non-rodent study, a segment II reproductive study as well as the standard International Committee on

Harmonization (ICH) battery of genotoxicity assays; and determine the immunosuppressive properties of the product.

5. Animal Pharmacology/Toxicology :

5.1 Mechanism of Action

In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP 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 G1 to the S phase of the cell cycle.

5.2 Animal Toxicology

Please refer to the Pharmacology-Toxicology Review dated August 20, 1999.

Thrombocytopenia and diarrhea were seen in pre-clinical animal studies. Slight (< 30%) decreases in platelets were seen in rats, and increases (< 40%) in fibrinogen were seen in rats and monkeys. Dose-related decreases in platelet counts have been observed in sirolimus-treated patients, although the magnitude of the reduction was such that no patients experienced severe bleeding and the thrombocytopenia rarely led to discontinuation of therapy. Fibrinogen levels were not measured in clinical trials.

Reviewer's note: In patients, sirolimus does cause a reduction of platelet counts, as was seen in the non-clinical studies.

Colitis and typhilitis, associated with chronic diarrhea, were observed in monkeys. These findings were considered secondary to either the immunosuppressive or the anti-microbial effect of sirolimus. Chronic diarrhea was accompanied by weight loss in the 3- and 6-month studies and was a contributing factor for a number of deaths or sacrifices *in extremis*. Diarrhea was more common at the higher dose of sirolimus (5 mg/day) used in the phase III trials. However, severe diarrhea, which might have been a symptom of colitis or typhilitis, was not seen in phase III trials.

In pre-clinical toxicology studies in rats and dogs, sirolimus was not associated with any histological evidence of renal toxicity.

Reviewer's note: However, pre-clinical toxicology studies were not done using sirolimus in combination with cyclosporine. Thus, the potential for sirolimus to enhance cyclosporine nephrotoxicity was not evaluated.

6.0 Clinical Background

6.1 Relevant human experience

Current therapy for rejection in renal transplantation requires therapy with steroids, cyclosporine and often a third agent such as azathioprine or mycophenolate mofetil (MMF). Steroids have side effects such as hyperglycemia, electrolyte abnormalities, osteopenia and cyclosporine causes hirsutism, gingival hyperplasia, renal insufficiency and contributes to atherosclerosis. Sirolimus offers the opportunity of adding a third drug which may work synergistically with cyclosporine and yet has different and some complementary toxicities to the more standard immunosuppressive modalities.

Renal transplantation has become the treatment of choice in the United States for patients with end-stage renal disease (ESRD). The leading causes of ESRD that lead to renal transplantation in the U.S. include diabetes mellitus, glomerulonephritis and hypertension. Stable renal transplant recipients, more than six months post-transplantation, represent the largest population receiving immunosuppressive therapy for prevention of allograft rejection. In 1998, the United Network for Organ Sharing (UNOS) reported that the total number of renal transplants performed in the U.S. was 11,990, which included 7,974 cadaveric transplants and 4,016 living donor transplants. The number of kidney-pancreas transplants performed in 1998 was 965. With available immunosuppressive therapy the one-, three- and five year graft survival rates for the first 56,835 cadaveric renal transplants reported to the UNOS Scientific Renal Transplant Registry between October 1987 through December 1996, for which a survival time could be determined, were 87.5%, 72.0% and 61% respectively. The corresponding results of transplantations from 21,597 living donors from October 1987 through December 1996, for which a survival time could be determined, were 93.5%, 85% and 76.6%.

These survival figures reflect current practice using a variety of immunosuppressive regimens, based on cyclosporine or tacrolimus, for the prophylaxis of renal allograft rejection. There is no consensus as to what constitutes the optimal immunosuppressive regimen in renal transplantation. Cyclosporine is always used with adrenal corticosteroids (dual therapy) which may be tapered over time. Initial therapy with azathioprine is often added to this regimen (triple therapy). Many U.S. kidney transplant centers may add a brief course of anti-lymphocyte antibody (induction therapy) to the triple regimen. In addition to corticosteroids, products approved for use in immunosuppressive regimens in renal transplantation in the U.S. include: Sandimmune® (cyclosporine U.S.P.), Neoral® (cyclosporine MODIFIED), SanCya® (cyclosporine MODIFIED), Imuran® (azathioprine), Cellcept® (mycophenolate mofetil), Prograf® (tacrolimus), ATGAM® (anti-thymocyte immunoglobulin), OKT3® (a murine monoclonal antibody against a human pan-T lymphocyte antigen approved for the treatment of steroid resistant rejection and also used as induction therapy). The two newest additions to the armamentarium of immunosuppressants include:

- 1) Simulect® (basiliximab)-a chimeric (murine/human) monoclonal antibody (IgG_{1k}), that binds to and blocks the interleukin-2 receptor (alpha)-chain (IL-2R(alpha), also known as CD25 antigen) on the surface of activated T-lymphocytes.
- 2) Zenapax ® (daclizumab) a humanized IgG₁ monoclonal antibody produced by recombinant DNA technology that binds specifically to the alpha subunit (p55 alpha, CD25, or Tac subunit) of the human high-affinity interleukin-2 (IL-2) receptor that is expressed on the surface of activated lymphocytes.

The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia. Hypertension may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Azathioprine is a purine analog which acts as an anti-metabolite. The principal and potentially serious toxic effects of azathioprine are hematological and gastrointestinal. These include, but are not limited to leukopenia and thrombocytopenia, which are dose-related. The risks of secondary infections and neoplasia are also significant.

Cellcept® (mycophenolate mofetil) is approved for the prevention of acute graft rejection and is used with cyclosporine and steroids as an alternative to azathioprine. The most serious toxic effects of Cellcept® are gastrointestinal and hematologic.

A significant adverse event associated with the use of Prograf® (tacrolimus) is post-transplant diabetes mellitus defined as the use of insulin to maintain normal blood glucose for 30 days, with less than 5 days interruption, in patients without a pre-transplant history of diabetes.

The most frequently reported side effects associated with Simulect® and Zenapax® were gastrointestinal symptoms such as nausea, diarrhea, and vomiting.

Rejection is a common phenomenon. Approximately 40-50% of renal transplant recipients will experience at least one rejection episode, commonly occurring during the first three months post-transplant. Steroids are usually the first line treatment for rejection. There are several acute and chronic side-effects that are associated with the use of steroids in transplantation. These include, but are not limited to, insulin-dependent diabetes, severe infection and osteoporosis.

There remains a need for additional immunosuppressive agents with non-redundant mechanisms of action and non-overlapping targets of toxicity.

6.2 Important information from related INDs and NDAs

This is a new molecule and class of immunosuppressant that was developed in the U.S. under IND [redacted] Phase II studies further characterized the safety profile of sirolimus and based on the rates of acute rejection and tolerability, the Applicant chose the sirolimus dose for the phase III studies. Toxicities include reductions in platelet and

white blood cell counts and hemoglobin and elevation of fasting triglycerides, cholesterol and LDH levels. No increased incidence rate of infection or malignancy was found.

6.3 Foreign experience

This product has not been approved for marketing in any country to date. Sirolimus has also been evaluated in non-IND studies in Europe, Australia and Canada. An application for authorization to market Rapamune® has been submitted to the European Union which includes the United Kingdom, Ireland, France, Belgium, Netherlands, Luxembourg, Germany, Finland, Sweden, Denmark, Italy, Spain, Greece, Austria and Portugal. National applications have also been submitted to Switzerland, Norway, Turkey and Canada.

6.4 Human Pharmacology, Pharmacokinetics (PK), Pharmacodynamics

Please refer to the Biopharmaceutics Review dated August 11, 1999.

The following is a summary of the basic PK characteristics of Rapamune® in renal transplant patients. Sirolimus pharmacokinetic activity has been determined following oral administration in healthy subjects, pediatric dialysis patients, hepatically-impaired patients and renal transplant patients. Sirolimus demonstrates:

- low bioavailability related to poor solubility
- food effect (Rapamune® should be taken in a consistent fashion with respect to food to minimize a potential source of pharmacokinetic variability)
- long half life ($t_{1/2}$) necessitates administration of a loading dose—overall, this may be a situation that is more forgiving to occasional lapses in compliance
- metabolism by P450 IIIA4 (CYP3A4) (this has implications with respect to potential for drug:drug interactions)
- extensively partitioned to formed blood elements (necessitates the need to measure whole blood levels) (mean B/P ratio = 36 among stable and post-transplant renal allograft patients)
- 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—this may have implications for potential drug-drug interactions.
- Rapamune® is mainly metabolized by intestinal and hepatic CYP3A4 to 7 major inactive metabolites. Excretion is mostly in the feces. Minimal excretion is in urine (2.2% in healthy volunteers) This leads to the implication that renal impairment is not expected to affect sirolimus blood levels. This is an important consideration in renal transplantation. Sirolimus has biphasic/triphasic elimination characteristics.
- There is limited data on the impact of race/age differences on the pharmacokinetics of Rapamune®. Further clarification of the impact of race and age on sirolimus pharmacokinetics is warranted.

- PK variability (The clinical implication is that a wide range of exposures is expected with a fixed daily dose). Sirolimus has a highly variable steady-state, oral-dose clearance i.e. intersubject CV% ~ 50 and intrasubject CV% ~ 26% among stable and post-transplant renal allograft patients).
- At present, there is no commercially available assay for Rapamune®. Although [redacted] were used during the clinical development of Rapamune®, therapeutic drug concentration monitoring (TDM) was not used in phase 3 clinical trials and no specific recommendations can be made about TDM at this time.
- Large steady-state volume of distribution (~ 1.6 L/kg in stable renal transplant patients).
- Prolonged terminal $t_{1/2}$ (~ 62 hours after multiple-dose administration in stable renal transplant patients).

Absorption:

Following oral administration, sirolimus is rapidly absorbed, with a mean time-to-peak concentration 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 low at approximately 14% and may be affected by food or concomitant administration of various medications. Sirolimus concentrations in stable renal transplant patients are dose proportional between 3 and 12 mg/m².

Reviewer's note : Pivotal studies 301 and 302 were performed with Neoral® as part of the immunosuppressive regimen. Neoral® enhances the absorption and increases the blood levels of Rapamune®. Consequently, Rapamune® must be taken 4 hours after the Neoral® dose. This need to separate the dosing of Neoral® and Rapamune® may be problematic in fostering patient compliance. In addition, clinicians will need to be alert for signs of drug toxicity in patients who may, for the sake of convenience, be taking Rapamune® concomitantly with Neoral®

There is large inter-subject variability with Rapamune® levels and in order to foster patient compliance, it will be important to ensure that Rapamune® is taken consistently with or without food. Fortunately, the long half-life of Rapamune®, may allow for the maintenance of therapeutic blood levels of the drug despite an occasional missed dose or despite an inconsistency in the timing of the dose

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 greater than 90% of the immunosuppressive activity.

Excretion

After a single dose of [¹⁴C] 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. 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.

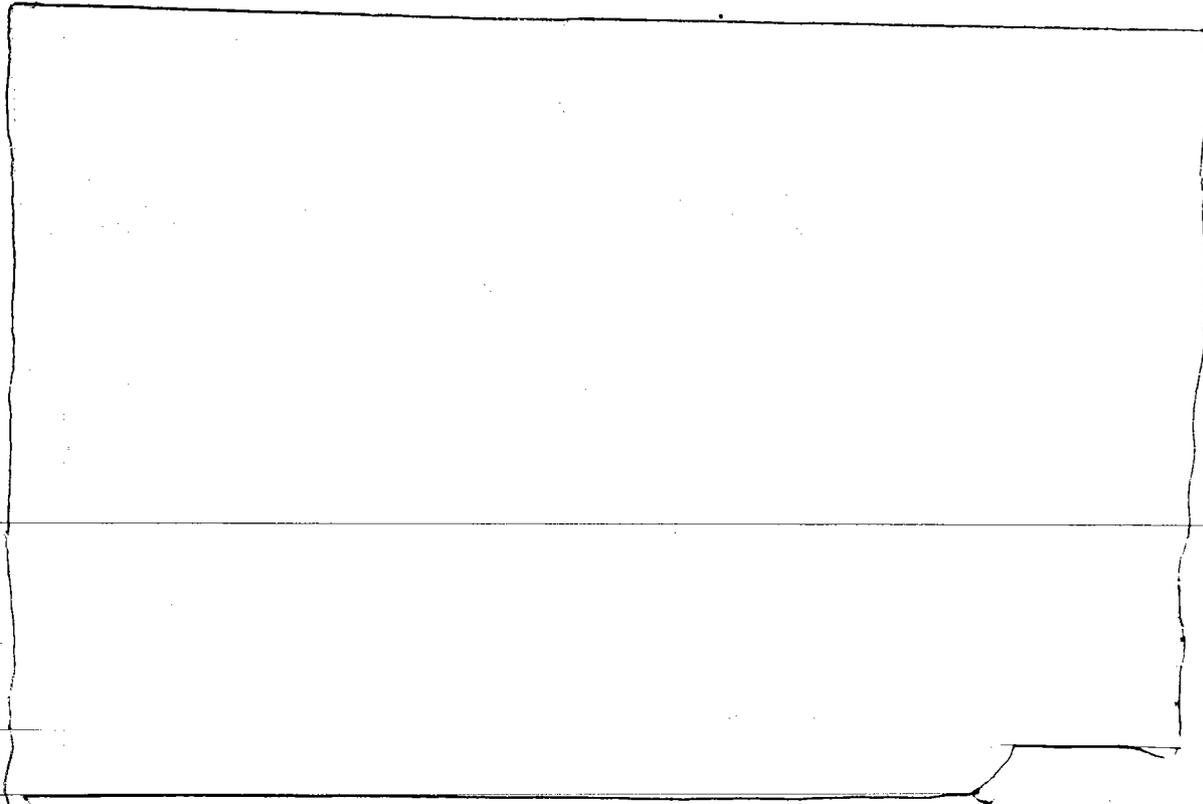
Reviewer's note: At this time there is no recommendation to adjust the dose of Rapamune® in patients with compromised renal function.

Special populations**Hepatic impairment:**

Patients with Child-Pugh class A or B hepatic impairment 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. Dosage adjustment is recommended for patients with mild to moderate hepatic impairment. However, the pharmacokinetics of sirolimus, in patients with severe hepatic dysfunction, is unknown.

Pediatric and Geriatric:

Limited pharmacokinetic data are available in pediatric and geriatric (>65 years of age) patients.





6.5 Other relevant background information

Letter dated December 15, 1998:

An end-of-Phase I meeting was held on April 18, 1994. The Agency agreed with proceeding to Phase II clinical studies and with the approach to study Rapamune® in combination with reduced and full doses of cyclosporine. No requirement to demonstrate the efficacy of Rapamune® as a single agent was necessary.

An end-of-Phase II meeting was held on December 15, 1995 and the Agency agreed with plans for Phase III controlled studies (301 and 302) and that it was essential to provide the primary evidence of efficacy for the indication of prophylaxis of organ rejection in renal transplant recipients. A composite endpoint consisting of the incidence of acute rejection, graft loss and patient survival at six months following transplantation was adopted as the first of two co-primary endpoints for both of these protocols. Patient and graft survival at twelve months would also need to be evaluated as a second co-primary endpoint. Rapamune® doses under study would be 2mg/day and 5mg/day and the comparators would be azathioprine (301) and placebo (302).

On March 21, 1996, protocols for two-year carcinogenicity studies in rats and mice and the rationale for dose selection was submitted and found to be acceptable.

Two pre-NDA meetings were held on March 31, 1998 and June 8, 1998 and agreement on the NDA content and formatting was reached.

6.6 Directions for Use

Sirolimus should be administered 4 hours after the morning dose of Neoral® (cyclosporine MODIFIED). If vomiting occurs less than 2 hours after the patient has received a dose of study medication, the dose should be re-administered at bedtime. Sirolimus and placebo should be diluted with 180 ml of water or orange juice. Grapefruit juice is not to be used because of the effect that it has on CYP3A4.

7.0 Description of Clinical Data Sources (both IND and non-IND)

7.1 Study Type and Design/Patient Enumeration, Demographics, Extent of Exposure

The efficacy and safety of sirolimus in preventing allograft rejection after kidney transplantation were evaluated in two large, active and placebo controlled phase III Wyeth-sponsored studies. These two pivotal trials, as well as important phase II clinical trials, are depicted in tabular form below (Tables 1, 2 and 3). It should be noted that the Division of Scientific Investigations (DSI) inspected two U.S. study 301 sites, two overseas study 302 sites and one U.S. study 302 site and found several minor problems with the conduct of studies 301 and 302. No major protocol deviations or violations were

identified that would preclude accepting data from any individual site. However, it should be noted that one study 301 investigator had a high rate of discontinuations at his site because he felt that when the patient's renal function began to worsen, it was imperative to discontinue study drug and initiate an alternative immunosuppressive regimen.

Table of Clinical Studies

Table 1

Phase III Studies: Adequate and Well-Controlled Studies in Renal Allograft Recipients

Protocol No.	Study Design	Concomitant Immunosuppressive Therapy	Comparator	Number of Patients:				
				SRL 2	SRL 5	AZA	Placebo	Total
0468E1-301-US	R,C,D,M	Corticosteroids, CsA	Azathioprine	284	274	161	0	719
0468E1-302-GL	R,P, D,M	Corticosteroids, CsA	Placebo	227	219	0	130	576
			Total	511	493	161	130	1295

R = randomized P = placebo control S = single-blind
M = multicenter D = double-blind
O = open label C = active control

Table 2

Supportive Phase II Study: Single-Blind Study in Renal Allograft Recipients, Including Steroid-Reduction Cohorts

Protocol No.	Study Design	Concomitant Immunosuppressive Therapy	Comparator	Number of Patients/Group:							
				A	B	C	D	E	F	G	Total
0468E1-203-GL	R,P,S	Corticosteroids, full or reduced dose CsA	Placebo/full dose CsA	25	20	27	26	24	27	35	184

Group A = CsA full concentration, placebo
Group B = CsA full concentration, sirolimus 1.0 mg/m²/d
Group C = CsA full concentration, sirolimus 3.0 mg/m²/d
Group D = CsA reduced concentration, sirolimus 1.0 mg/m²/d
Group E = CsA reduced concentration, sirolimus 3.0 mg/m²/d
Group F = CsA reduced concentration, sirolimus 5.0 mg/m²/d
Group G = sirolimus 3 mg/m²/d for one month followed by 1 mg/m²/d for 11 months; CsA full concentration, corticosteroids withdrawn after 4-8 weeks

R = randomized P = placebo control S = single blind
M = multicenter D = double-blind
O = open label C = active control

Table 3

Supportive Phase II Studies: Sirolimus as Concentration-Controlled, Base Therapy in Renal Allograft Recipients

Protocol No.	Study Design	Concomitant Immunosuppressive Therapy	Comparator	Treatment		Number of Patients:		
				Sirolimus	CsA	SRL	CsA	Total
0468E1-207-US	R,O,M	Corticosteroids, azathioprine	CsA	Target trough levels 30 ng/mL for 2 months, then 15 ng/mL	Target trough levels 200-400 ng/mL for 2 months, then 100-300 ng/mL	41	42	83
0468E1-210-EU	R,O,M	Corticosteroids, mycophenolate mofetil	CsA	Concentration controlled	Concentration controlled	40	38	78

R = randomized

M = multicenter

O = open label

Reviewer's note: The number of subjects and duration of follow-up for studies 301 and 302, at the proposed doses of 2 and 5 mg per day, appears sufficient to evaluate the safety of these doses. Study 203, conducted in the US, was used to support dose selection in phase III, was reviewed under the U.S. IND and will not be discussed further in this review.

Supportive phase II studies, 207 in the US and 210 in Europe (EU) are still ongoing and do not pertain to the proposed use of sirolimus in combination with cyclosporine. Although they will not be discussed any further in this review, they were taken into consideration when evaluating intrinsic toxicities associated with sirolimus in human subjects.

8. Clinical Studies

8.1 Indication Sirolimus for the prevention of acute rejection in renal transplantation.

8.1.1 Reviewer's Trial # 1; Applicant's protocol 0468E1-301-U.S.

8.1.1.1 Objective/Rationale

The primary objectives of this study were to compare the safety and efficacy of two dose levels of sirolimus versus azathioprine, administered concomitantly with standard immunosuppressive therapy (cyclosporine and corticosteroids) in patients receiving renal allografts.

8.1.1.2 Design

The study was designed as a double-blind, multicenter (40 centers), randomized (2:2:1), double-dummy, two part comparative study using azathioprine as an active control. Notably, patients were randomized 24-48 hrs. post-transplant. There were 3 treatment groups designated as sirolimus 2mg, sirolimus 5mg or azathioprine treatment. The study was stratified by center and by race (black or non-black) within each center. A strength of study 301 was its enrollment of adequate numbers of African-American patients. Patients were assigned using the CORE system of automatic trans-telephonic randomization (computerized randomization/enrollment) Randomization at 24-48 hours post-transplant may eliminate some patients with surgical complications but it also may eliminate higher risk patients with delayed graft function. The objective endpoints for both study 301 and 302 included a composite endpoint of acute rejection, graft loss (defined as nephrectomy or dialysis for 56 or more consecutive days) or death at 6 months and patient and graft survival at 12 months.

8.1.1.3 Protocol

This was a phase III, U.S., multi-center, active-controlled, randomized, double-blind, double-dummy, parallel group study. Neoral®, azathioprine and prednisone were chosen as the comparator, as this regimen represented the standard of care at most participating US phase III renal transplant sites. The study was stratified at the time of randomization by ethnic origin because of the increased risk for acute rejection and graft loss experienced by black transplant recipients. The first of two co-primary endpoints in this study was efficacy failure, defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death within the first six months after transplantation. The study was also designed to evaluate the equivalence of sirolimus and cyclosporine with respect to one-year patient and graft survival as a second co-primary endpoint.

Reviewer's note: Equivalence studies are susceptible to the effect of crossover from one treatment group to another which may obscure a therapeutic difference, if subjects in both treatment groups end up receiving similar therapy for a prolonged period of time.

Selection of dose was based on preliminary results of a phase II renal prophylaxis study (0468E1-203-GL) and analysis of this data did not show an efficacy dose-response between 1mg/m²/day, and 3mg/m²/day, although the number of patients per group was small (about 25). Inter- and intra-patient trough concentration and AUC variability might have obscured any impact of minor dose variations based on body surface area calculations. Therefore, two fixed dose levels (2mg/day and 5 mg/day) which represent central values for each of the two surface area dose levels studied in Phase II, were chosen for this Phase III study.

Reviewer's note: There was discussion regarding the use of therapeutic drug monitoring (TDM) with sirolimus; however the Applicant did not wish to incorporate TDM as part of its initial drug development plan.

8.1.1.3.1 Population

Study 301 was conducted in the U.S.

Reviewer's note: A strength of study 301 was its enrollment of adequate numbers of African-American patients. The African-American segment of the U.S. renal transplant population is 21.3% according to 1998 United Network for Organ Sharing (UNOS) data. In study 301, African-Americans comprised 23.1% of the study population. In addition, notable exclusions from the protocol included multi-organ transplants, re-transplants, patients with high panel reactive antibody (PRA) and patients who required anti-lymphocyte antibody induction. Thus, patients who would have represented "high risk" recipients were excluded from the study.

Inclusion Criteria

1. Age: ≥ 13 years of age; weight ≥ 40 kg.

Reviewer's note: Additional studies will need to be done to determine the optimal dose in children < 13 years of age and in patients who weigh < 40 kg.

2. End-stage renal disease, with patients receiving a primary renal allograft from a cadaveric donor (including en-bloc kidneys), from a living-unrelated donor, or from a living-related (excluding HLA-identical) donor.
3. Women who are of childbearing potential must have a negative pregnancy test before study medication administration and agree to use a medically acceptable contraceptive throughout the treatment period and for 3 months after discontinuation of study medications. Any woman becoming pregnant during the treatment period must discontinue using study medications.
4. Total white blood cell count $\geq 4 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, fasting triglycerides ≤ 5.5 mmol/L (≤ 489 mg/dl) and cholesterol ≤ 9.1 mmol/L (≤ 353 mg/dl) before study drug administration.

Reviewer's note: Leukopenia and hyperlipidemia were adverse effects identified in the phase II trials of sirolimus.

5. Signed informed consent (parent or legal guardian must provide written consent for patients < 18 years of age).

Exclusion Criteria

1. Evidence of systemic infection before administration of study medications.
2. Presence of unstable angina, recent myocardial infarction (within past 6 months), or use of ongoing maintenance therapy for life-threatening arrhythmia.
3. History of malignancy within 10 years of enrollment into the study (with the exception of adequately treated basal or squamous cell carcinomas of the skin).
4. Use of any investigational drug within 4 weeks of administration of study medications.
5. Current use of immunosuppressive agents other than those described in Treatment Administration, section 6.4.1. of the NDA.
6. Current use of cytochrome P450 inducers/inhibitors as described in Attachment 2 of the NDA ---unless these drugs were discontinued before transplantation. These drugs affect the metabolism of both sirolimus and cyclosporine.
7. Current use of terfenadine, cisapride, astemizole or pimozone unless these drugs were discontinued before transplantation. These drugs, when given in conjunction with cyclosporine, may cause cardiac arrhythmias.
8. Use of antibody induction therapy at the time of transplantation.

Reviewer's note: Approximately, 50% of the renal transplants in the U.S. are performed using induction therapy. This restriction will influence the type of dosing recommendations and indications that can be made in the label.

9. Active gastrointestinal disorder that may interfere with drug absorption.
10. Evidence of infiltrate, cavitation or consolidation on chest x-ray during pre-study screening.
11. Known hypersensitivity to macrolide antibiotics.
12. Known hypersensitivity to azathioprine or 6-mercaptopurine.

Removal of Patients From Therapy or Assessment

Patients who discontinued using the study medications for any reason were not replaced. Patients who were randomly assigned but did not receive study medications and patients who received study medications but discontinued using them before the end of the treatment period were not withdrawn from the study and were followed up at 1 month post study discontinuation and at months 6,12, and 15. Visits included vital signs, physical exam, serum creatinine and blood urea nitrogen (BUN). Patient and graft survival data was to be noted at month 6,12,24 and 28. Follow-up information and the date of withdrawal were recorded on the patient's case report form. Adverse events were recorded at the time of discontinuation and 1 month after discontinuation of study medication.

Reviewer's note: Study 301 was a two year study but the Division agreed that 12 month data would be sufficient for the NDA.

Procedures

Sirolimus was administered with a loading dose that was equal to three times the maintenance dose (SRL 6 mg or SRL 15 mg) followed by the fixed daily maintenance dose (SRL 2mg/day or SRL 5 mg/day). The daily dose was administered four hours after the morning dose of Neoral®—since exposure to sirolimus is increased when co-administered with Neoral®. This effect is attenuated when administration of the sirolimus and Neoral® is separated by at least 4 hours. If vomiting occurred less than 2 hours after the patient had received a dose of study medication, the dose was re-administered at bedtime. Sirolimus and placebo were to be diluted with 180 ml of water or orange juice.

Concomitant medications

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

On days 1-4, corticosteroids were tapered down from 500 mg to 120 mg IV methylprednisolone, on day 5, prednisone 80 mg PO was given followed by tapering doses of PO prednisone until a dose of 10 mg/day was attained by month 6 and between 5-10 mg/day PO prednisone by month 12.

If the patient was unable to initially take PO well, Sandimmune® IV was administered for the first 48 hours post-transplant. Otherwise the patient was begun on Neoral® dosed according to the target trough level scheme depicted below:

Cyclosporine dosing for study 301:

Month 1	200-350 ng/ml
Month 2-3	200-300 ng/ml
≥ Month 3	150-250 ng/ml

Reviewer's note: *These cyclosporine target trough levels represent the customary concentrations used for cyclosporine in standard triple regimens. However, it should be noted, that the majority of study patients actually maintained target trough levels above the upper bound of the recommended ranges. This may reflect investigator uneasiness with the double-blind aspect of this trial.*

Azathioprine, the active comparator in study 301, was dosed at 2-3 mg/kg/day.

Reviewer's note: *The active control, azathioprine, was adequately dosed. However, the use of azathioprine in Study 301 was different than its use in many transplant centers which may often discontinue azathioprine after 3-6 months.*

Rejection episodes, as determined by serum creatinine and biopsy, were to be treated similarly in all arms of the study. The first episode of documented rejection was to be treated with a steroid pulse and if this was unsuccessful the investigator determined the next appropriate plan of action i.e. whether to use antibody therapy or pursue an alternative immunosuppressive regimen.

Therapy required during the treatment period

Prophylaxis for *Pneumocystis carinii pneumonia* (PCP) during the first year utilized Bactrim® or suitable alternative.

Antibacterial prophylaxis against urinary tract infection (UTI) was required for all patients for up to 6 weeks post-transplantation if they could not tolerate Bactrim.®

Cytomegalovirus (CMV) prophylaxis was center-specific and was required in "high risk" CMV negative recipients of CMV positive donor kidneys and was recommended for lower risk patients. Prophylactic regimens included oral ganciclovir or oral acyclovir with or without immunoglobulin preparations such as CMVIG or IVIG.

Recommended therapy during the treatment period

Prophylaxis against oral candidiasis for 3 months, utilizing either clotrimazole or nystatin.

Fluconazole was not allowed.

Reviewer's note: *These are adequate measures for the prophylaxis of infection post-transplant.*

8.1.1.3.2 Co-primary Endpoints

The first co-primary efficacy endpoint was the rate of efficacy failure in the first 6 months (194 days) after transplantation. Efficacy failure was defined as the first occurrence of acute rejection (confirmed by biopsy within 48 hours), graft loss necessitating maintenance dialysis for >56 days or death. The second co-primary endpoint was patient and graft survival at one year.

Reviewer's note: *These are considered appropriate endpoints to evaluate efficacy and are reasonably resistant to bias if the 12 month follow-up is complete and the primary analysis is conducted according to intent-to-treat.*

Reviewer's note: *On April 14, 1999, Wyeth-Ayerst notified the Division of a programming error in the SAS program that was used to create the efficacy analysis data-sets. This error caused an under-reporting of biopsy-confirmed rejections. When the efficacy analysis data-sets were created, the acute rejections for investigators with alphanumeric identification numbers were not included. Upon further inspection of the raw data listings of the biopsy findings, by the FDA statistician, several other*

biopsy-proven rejections were noted. These rejections were not included in the original analysis because the biopsy was not performed within the protocol stated two days of start of treatment for presumed rejection. It was agreed at a May 7, 1999 with Wyeth-Ayerst that these events should be included in the analysis of acute rejection. In addition, from the time the original blinded database was frozen, there were a number of changes to the efficacy outcome designations for a number of patients due to ongoing data clarification. Therefore, the analyses performed in this review are based on data-sets that were received on May 17, 1999. These data-sets were created from a more extensive updated database and used the expanded treatment window for acute rejection. This analysis is denoted as the "inclusive analysis" in the revised ISE submitted on June 1, 1999. (Please see the Statistical Review dated August 20, 1999).

Secondary efficacy endpoints included time to first acute rejection and treatment failure, histological grade of the first acute rejection episode, use of antibody therapy for the first acute rejection episode, incidence of infections, malignancies and post-transplant lymphoproliferative disease (PTLD).

Reviewer's note: These secondary endpoints are of interest in transplantation. However, because of the multiple comparisons, it may not be possible to draw reliable conclusions from these.

To estimate concurrence between readings by the local pathologists and a blinded central reviewer, a random 20% sample of the total number of biopsies performed across all centers for the purpose of diagnosing acute rejection within the first 6 months after transplantation was provided to the central pathologist for review. Tables of the agreement for each center were provided and Cohen's Kappa, a summary statistic of agreement with 95% confidence interval, was used to measure this agreement.

Reviewer's note: It should be noted that the evaluation of acute rejection using a standardized histologic grading system (Banff criteria) was a strength of this study. A correlation between the local readings from a central pathologist was made and the Kappa statistic of agreement showed satisfactory agreement between the local and central pathologist in each study. However, the histologic reading of the local pathologist was utilized for both the purpose of the efficacy analysis and to guide blinded treatment decisions.

8.1.1.3.3 Statistical considerations

Please refer to the Statistical Review dated August 20, 1999.

The primary analysis of efficacy failure for each study consisted of comparisons between each dose of Rapamune® and the comparator done by using the Cochran-Mantel-Haenszedl (CMH) statistic stratified by investigator. All patients assigned to treatment were included in this analysis ("Intent to treat" or ITT). Comparisons of each dose of Rapamune® with control therapy were made using the Bonferroni correction to the alpha level. Thus, to maintain an overall probability of type I error of 0.05, an adjusted

significance level of 0.025 was used for each comparison. Patients defined as lost to follow-up were scored as efficacy failures, regardless of treatment assignment.

For the purposes of determining sample size, efficacy failure rates at 6 months were estimated to be 18% for Rapamune® treated patients and 36% for the azathioprine control group. The randomization ratio was 2:2:1, Rapamune® 2 mg/day to Rapamune® 5 mg/day and control groups, respectively. For study 301, 234 patients were needed in each of the two Rapamune® treatment groups and 132 patients in the azathioprine control groups, in order to have 90% power to declare a significant difference in each comparison under the conditions described; a minimum total of 420 patients was required. Study 301 enrolled patients beyond the minimum number stated in the protocol in order to ensure that the data from a sufficient number of patients, at or above the recommended Rapamune® dose level, would be available for the safety analysis.

Reviewer's note: Please see the Statistical Review for further details.

8.1.1.4 Results

8.1.1.4.1 Patient Disposition, Comparability

Three different populations were defined before unblinding the studies for the determination of efficacy and safety:

- 1) intention to treat
- 2) efficacy subpopulation and
- 3) safety population.

The primary focus of the efficacy analyses in this review is on the intention-to-treat population; that is all patients who are randomized to therapy.

An analysis of the primary endpoint was also performed on an efficacy subgroup of patients who had taken at least the first five consecutive doses of study medication. The purpose of this analysis was to determine the efficacy of the medication in patients who have had an adequate amount of exposure to study medication. Patients who are lost to follow-up in these and subsequent analyses have their endpoints scored as events, regardless of therapy, unless otherwise stated.

The population of patients who have received at least one dose of study medication was the focus of the safety analyses and this included 1260 of the 1295 randomized study patients for study 301 and 302. The safety population for study 301 and 302 included 976 patients who received Rapamune®, 160 patients who received azathioprine and 124 patients who received placebo.

Reviewer's note: FDA's primary efficacy analysis was based on the intent-to-treat population. FDA concurred with the choice of safety population.

Investigators Study 301

There were forty U.S. investigators/study sites for study 301. Enrollments ranged from 3 patients at the University of Miami in Florida to 75 patients at the University of Texas in Houston. Two sites failed to enroll any patients. Study site 30146 had 20/37 patients (54.1%) prematurely discontinue study medication. The Division of Scientific Investigation (DSI) was requested to investigate this site and found several discrepancies but none that would exclude the use of data from this site in the final analysis. The main reasons for discontinuation of study medication at this site included:

SRL 2 mg (n=11)	5 adverse reactions, 1 unsatisfactory response, 2 patient requested to change, 1 protocol violation and 2 other medical events
SRL 5 mg (n=5)	2 adverse reactions, 1 unsatisfactory response, 1 other medical event, 1 patient request to change
Azathioprine (n=4)	3 adverse reactions, 1 unsatisfactory response

Reviewer's comment: *The reasons for discontinuation at this site were not unusual and did not reflect a low threshold for discontinuing patients. I am uncertain regarding the exact number of patients who discontinued study drug and were unblinded.*

Patient Demographics

Study 301 was conducted at 40 centers in the United States: 38 centers enrolled patients. A total of 719 patients were enrolled in the study and randomized to one of the three treatment groups: 2 mg/day Rapamune[®] (n=284), 5 mg/day Rapamune[®] (n=274), and azathioprine (n=161). 710 patients received at least one dose of study drug and nine patients were randomized into the study but did not receive at least one dose of study medication (3 patients on Rapamune[®] 2 mg/day, 5 patients on Rapamune[®] 5 mg/day, and 1 patient on azathioprine). Please see Table 4 below and the Reviewer's note.

Table 4

Patient Accounting by Treatment Group Study 301

Study 301	SRL 2	SRL 5	AZA
Patients randomized	284	274	161
Patients enrolled	281	269	160

Reviewer's note: *Nine study 301 randomized patients failed to enroll due to non-compliance, protocol violation, patient treated with anti-lymphocyte antibody, and myocardial infarction during surgery. These nine patients were included in the six month primary analysis of efficacy and were evaluated according to their intent to treat assignment: SRL 2 (1 graft loss, 2 "no events"), SRL 5 (1 graft loss, 1 rejection, and 3 "no events") and AZA (1 "no event"). Twelve month follow-up for patient and graft survival was also obtained on these nine patients who randomized and failed to enroll.*

Over the course of the 12 month treatment period following transplantation, several patients discontinued study medication. Discontinuation was defined as having study drug held for ≥ 21 days. See Table 5 (below) which summarizes the reasons for discontinuation and the numbers of patients who discontinued per treatment assignment for study 301. Patients who discontinued study medication were followed-up at one month for collection of adverse event data and were directed to return for follow-up at months 6, 12, 15, 24, and 28 to collect data on renal function and patient and graft survival.

Table 5

% Study 301 Patients who discontinued during the treatment phase (12 months)¹

Reason	SRL 2 (n=284)	SRL 5 (n=274)	AZA (n=161)	Fisher's exact p- Value
Adverse reaction	27 (9.5)	43 (15.7)	18 (11.2)	0.0778
Failed to return	4 (1.4)	1 (<1)	1 (<1)	0.4541
Other medical event	21 (7.4)	28 (10.2)	10 (6.2)	0.2985
Other non-medical event	9 (3.2)	3 (1.1)	5 (3.1)	0.1884
Patient/subject request	17 (6.0)	12 (4.4)	9 (5.6)	0.6834
Protocol violation	15 (5.3)	15 (5.5)	4 (2.5)	0.3111
Unsatisfactory response-efficacy	42 (14.8)	29 (10.6)	35 (21.7)	0.0073
Total	135 (47.5)	131 (47.8)	82 (50.9)	0.7675

¹ Twelve month data is from the Applicant's analysis found in the Advisory Committee Briefing Package dated 7/27/99.

Reviewer's note: Overall, the rates of discontinuation in study 301 were high (47.5-50.9%) but similar among treatment groups. The most frequent reason for discontinuation in the Rapamune® 2 mg/day group (SRL 2) and in the azathioprine control (AZA) was unsatisfactory efficacy response. The most frequent reason for discontinuation in the Rapamune® 5 mg/day group (SRL 5) was adverse event. These relatively high rates of discontinuation may reflect investigator uneasiness regarding the double-blind design of the trial. High rates of discontinuation may also impact the evaluation of differences in patient and graft survival and renal function parameters at 12, 24 and 28 months post-transplant. Patients who discontinued study drug were included in the six month efficacy analysis and evaluated according to their intent-to-treat study drug assignment. The Applicant submitted a "line listing" of all discontinuations for study 301 (see "Response to FDA for Information" dated May 13, 1999). I believe the numbers and reasons for study 301 discontinuations, listed in Table 5, to be correct.

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Demographics

Table 6
Patient Demographics Study 301¹

	Rapamune® 2 mg/day (%)	Rapamune® 5 mg/day (%)	Azathioprine- (%)	P-value
# Patients	284	274	161	-
Gender (N)				0.001
Female	76 (26.8)	103 (37.6)	71 (44.1)	
Male	208 (73.2)	171 (62.4)	90 (55.9)	
Age mean (SD)	44.9 (13.6)	46.9 (13.0)	45.4 (13.0)	0.173
min, max	16, 79	13, 76	12, 69	
Race (N)				0.935
Caucasian	160 (56.3)	154 (56.2)	92 (57.1)	
Black	63 (22.2)	61 (22.3)	42 (26.1)	
Hispanic	48 (16.9)	43 (15.7)	14 (8.7)	
Oriental (Asian)	7 (2.5)	10 (3.6)	10 (6.2)	
Other	6 (2.1)	6 (2.2)	3 (1.9)	
Donor Source (N)				0.054
Cadaver	180 (63.4)	167 (61.0)	119 (73.9)	
Living (Related)	86 (30.3)	83 (30.3)	33 (20.5)	
Living (Unrelated)	18 (6.3)	24 (8.8)	9 (5.6)	

1. FDA analysis—see Statistical Review.

Table 6 shows demographic and baseline characteristics for all randomized patients. There were no statistically significant differences across treatment groups with the exception of gender. A significantly ($p < 0.001$) higher proportion of females were assigned to the azathioprine (43%) than to the Rapamune® groups (26.8% for 2 mg/day, 37.6% for 5 mg/day). The majority of the patients were male and Caucasian. The source of the donor allograft was primarily cadaveric. The descriptive variables, gender, race, and donor source were evaluated using CMH tests stratified by investigator. Age was evaluated using ANOVA with treatment and investigator as factors.

Reviewer's note: Despite differences in gender across treatment groups, there was no significant difference in weight. Therefore, the gender differences across treatment groups would not be expected to impact either drug exposure or the results of the efficacy analysis for study 301 which utilized a fixed dose of Rapamune®.

Baseline Characteristics

The main etiologies for renal failure were hypertension, diabetes mellitus and glomerulonephritis and this is representative of the reasons for end stage renal disease (ESRD) in the United States population (see Table 7)