DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS HFD-590

Medical Officer Review

PEDIATRIC EXCLUSIVITY DETERMINATION REQUEST - PEDIATRIC STUDY REPORTS-

1 GENERAL INFORMATION

1.1 SPONSOR IDENTIFICATION

Name: Wyeth Pharmaceuticals

Address: P.O. Box 8299 Philadelphia, PA 19101-8299

Name of Contact: Randall B. Brenner Associate Director Worldwide Regulatory Affairs (484) 865-3792 brenner1@wyeth.

1.2 SUBMISSIONS / REVIEW DATES

Patent Expiration date: September 15, 2004

Date of Submission: September 13, 2004

CDER Stamp Date: September 15, 2004

Date Received by Medical Officer: September 15, 2004

Date of Pediatric Exclusivity Review Board Meeting: November 17, 2004

Date of Written Review completed: March 7, 2005

1.3 FDA REVIEWERS:

Medical Team Leader: M. Cavaille-Coll (HFD-590)

Medical Reviewer: A. Hernandez (HFD-590)

Biopharm reviewer: Gerlie Geieser (HFD-590)
Biopharm. Team Leader: Philip M. Colangelo (HFD-590)

Statistical Reviewer: C. Dixon (HFD-725)

Project Manager: Saville Rebecca (HFD-590)

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1.4 ABREVIATIONS AND DEFINITIONS:

Therapy: In this application the term therapy was used interchangeably for the term regimen i.e. immunosuppressive therapy or immunosuppressive regimen

SRL: Sirolimus
TAC: Tacrolimus (Rapamune®)
CsA: Cyclosporine
MMF: Mycofenolate Mofetil (CellCept ®)
CS: Corticosteroids

High Risk Patients: Renal transplant recipients who participated in study 217. This group of patients had previously experienced at least 1 prior episode of acute rejection or had histological evidence of chronic allograft nephropathy (chronic rejection) or both. As a group, these patients had reduced renal allograft function at the time of enrollment.

Standard therapy: In study 217 this term was assigned to the immunosupresive regimens received by the control group and included the following regimens:

- TAC+CS (Double Therapy)
- CsA+CS (Double Therapy)
- TAC + Aza +CS (Triple Therapy)
- CsA + MMF + CS (Triple Therapy)

Standard therapy was also referred as standard CsA or tacrolimus-based therapy.

Sirolimus plus Calcineurine Inhibitor based therapy: In study 217 this term was assigned to the immunosuppressive regimens received by the test group and included :

- SRL+ TAC + CS
- SRL +CsA + CS

As observed this regimens included corticosteroids.

Efficacy Failure (Primary endpoint): In study 217, efficacy failure was defined as the composite of the first occurrence of biopsy-confirmed acute rejection, graft loss, or death.

1.5 DRUG IDENTIFICATION

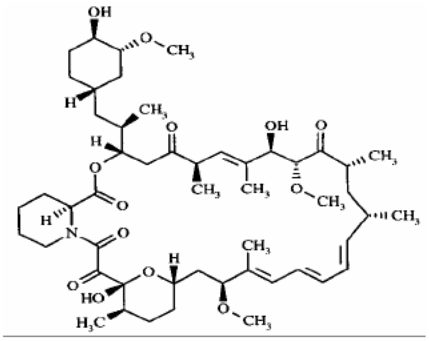
Generic Name: Sirolimus (also known as rapamycin)

Proposed Trade Name: Rapamune®

Chemical Name:

(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]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4H,6H,31H)-pentone.

Chemical Structure:



1.6 PHARMACOLOGIC CATEGORY*:* Immunosuppressive Agent

1.7 DRUG INDICATIONS:

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 immunologic risk cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune® dose should be increased to reach recommended blood concentrations.

1.8 PRESENTATION:

Rapamune® (sirolimus) Oral Solution 1 mg/mL (NDA-21-083)

Rapamune® (sirolimus) Tablets:

1 mg, white, triangular-shaped tablets (NDA 21-110)

2-mg, beige triangular-shaped tablets (sNDA 21-110/s-003)

5-mg tablet (sNDA 21-110/S-018)

1.9 RELATED DRUGS:

There are currently no related drugs approved.

1.10 IND DOCUMENTS SUBMITTED AND REVIEWED:

SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

This document was submitted entirely in electronic Common Technical Document (eCTD) format:
Module 1 – US FDA Regional Administrative Information
Module 2 – Common Technical Document Summaries
Module 5 – Clinical Study Reports (including CRFs)

2 EXECUTIVE SUMMARY

The original Pediatric Written Request (WR) for Rapamune was issued on 15 Sep 1999 and addressed the fact that limited pharmacokinetic data were available in children.

Wyeth's response to the pediatric Written Request for Rapamune included two studies:

- Protocol 0468E1-217-US, "An Open-Label, Comparative Study of the Effect of Sirolimus versus Standard Treatment on Clinical Outcomes and Histologic Progression of Allograft Nephropathy in High Risk Pediatric Renal Transplant Patients,"
- Protocol 0468H1-315-US, "A Double-Blind Randomized Trial of Steroid Withdrawal in Sirolimus and Cyclosporine-Treated Primary Transplant Recipients." ***(pharmacokinetic portion)***

The WR was amended on 17 May 2004 (To include categorization of patients by race and ethnicity) and on 24 May 2004 (To allow to obtain pharmacokinetic (PK) profiles from patients across multiple studies).

Protocol 217 was a randomized study in high-risk pediatric renal allograft recipients[1] that compared the safety and efficacy of sirolimus (SRL) plus a Calcineurin Inhibitor (C Inh)[2] and corticosteroids (CS) versus double therapy (CsA or TAC and CS) or triple therapy (CsA or TAC plus azathioprine or MMF and CS).

Efficacy was to be assessed by comparing the composite endpoint of the first occurrence of biopsy-proven acute rejection, graft loss, or death after 36 months of treatment.
Efficacy failure in the intention-to-treat (ITT) population (n=102) was numerically more frequent in subjects randomly assigned to receive the combination of sirolimus and a C Inh than in the subjects allocated to standard therapy (29/65, 44.6% versus 12/37, 32.4%, respectively). When comparing only subject 18 years old or younger (24/53, 45.3% versus 11/25, 44.0%,

[1] Eligible subjects were those with ≥ 1 episode of acute rejection as well as those subjects with biopsy-proven chronic rejection.

[2] Cycolsporine (CsA) or Tacrolimus (TAC)

respectively) efficacy failure rates were similar. (Please see **Table 8-1, Efficacy Failure Rates, ITT analyses at 36 months,** Section # 8, of this review)

Adverse events such as abdominal pain, fever, abnormal renal function, and urinary tract infection (UTI) were significantly more common in the sirolimus treatment cohort compared with standard therapy. UTI rates were 15% versus 1% in the sirolimus combination group versus the control group, respectively.
Overall, the remaining adverse event rates were numerically similar in both randomized groups.

Pharmacokinetics data were collected across studies 217 and 315. These studies targeted sirolimus whole blood concentrations from 5 to 15 ng/mL, and 10 to 20 ng/mL, respectively (chromatographic method).

Sirolimus and CsA Regimen:
Younger children had overall lower sirolimus dose normalized exposure apparently due to higher clearance.
A strong correlation at steady-state between whole blood sirolimus C_{min} and AUC values were observed for all treatments and regimens. We agree that these results indicate that sirolimus trough concentrations were adequate surrogates for sirolimus exposure. (See Section 7 of this review and Biopharmaceutics review for further details)

Conclusions:

- ***We agree with the sponsor that treatment of subjects with a prior history of acute rejection and/or chronic allograft nephropathy with the combination of sirolimus and a calcineurin inhibitor does not confer greater protection against recurrent acute rejection or progression of chronic allograft nephropathy than calcineurin inhibitor-based immunosuppression alone and may increase the risk for hyperlipidemia and faster renal function deterioration.***
- ***In the renal transplant population, the safety profile of sirolimus in children and adolescents appears to be similar to that for adults.***
- ***The chronic use of cyclosporine together with Rapamune® as a maintenance regimen is no longer an acceptable in renal transplant recipients at low to moderate risk for rejection and the same statement appears to be true for children due to the resulting increased impairment in renal function.***
- ***The sponsor fulfilled the request for characterizing PK profiles of sirolimus in children and these studies qualify Rapamune for an extension of exclusivity under section 505A.***
- ***The results of these studies support the addition of information to the Rapamune labeling regarding safety and pharmacokinetics in children.***
- ***Information on the use of sirolimus in the children studied, and its potential hazards should be included in the label.***

3 INTRODUCTION

The United Network for Organ Sharing (UNOS) registry data indicates that 690 of the 14,671[3] (4.7%) renal transplants in the United States were performed in children 17 years old or younger. During the last three years approximately 450 kidney transplants are performed annually in the U.S. in children between 11 to 17 years old. Approximately 140 to 150 kidney transplant are annually performed in the age group of 6 -10 years and similar number for the 1 - 5 years age group.
Kidney transplants in children less than one year of age are extremely rare.

Despite all the improvements made in decreasing acute rejection rates, graft survival rates beyond 1 year after transplantation, remain unchanged and chronic rejection remains as the major cause of graft loss, accounting for 32.5% of all graft losses[4].

The chronic use of calcineurin inhibitors (CInh.) has been considered and important contributing factor for the development of chronic rejection and loss of renal function.
The use of mTOR inhibitors, such as Sirolimus, has been considered an important alternative to avoid or limit the chronic use of CInh.

At the present, Rapamune® (sirolimus) is indicated for the prophylaxis of organ rejection in renal transplants recipients at low to moderate immunologic risk. It is recommended that Rapamune be used initially in a regimen with CsA and CS then cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune® dose should be increased to reach recommended blood concentrations. We agree with the applicant that the safety and efficacy of such regimen have not been established in pediatric subjects below the age of 13 years. (b) (4)

4 REGULATORY HISTORY

4.1 Pediatric Written Request:

The original Pediatric Written Request (WR) for Rapamune was issued on 15 Sep 1999.
After the Best Pharmaceuticals for Children Act (BPCA), the WR was reissued unchanged on 03 Jul 2002 under the provisions of the BPCA.

On 17 May 2004, the WR was amended to require categorization of patients by race and ethnicity. A second amendment to the WR was issued on 24 May 2004 to allow pharmacokinetic (PK) profiles to be obtained from patients across multiple studies, and to revise the numbers of PK patients required in younger age groups.

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[3] Based on OPTN data as of February 25, 2005, http://www.optn.org/latestData/rptData.asp

[4] Seikaly M, Ho PL, Emett L, et al. The 12th annual report of the North American Pediatric Renal Transplant Cooperative Study: renal transplantation from 1987 through 1998. *Pediatr Transpl.* 2001;5:215-231.

Two studies that were performed in response to the pediatric Written Request for Rapamune:

- Protocol 0468E1-217-US, "An Open-Label, Comparative Study of the Effect of Sirolimus versus Standard Treatment on Clinical Outcomes and Histologic Progression of Allograft Nephropathy in High Risk Pediatric Renal Transplant Patients,"
- Protocol 0468H1-315-US, "A Double-Blind Randomized Trial of Steroid Withdrawal in Sirolimus and Cyclosporine-Treated Primary Transplant Recipients." ***(pharmacokinetic portion)***

4.2 Rapamune® Regulatory Background:

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.
Rapamune® was originally approved only for use in a regimen including cyclosporine and corticosteroids. The combination of Rapamune® and standard cyclosporine dosing was found to be associated with an increased incidence of renal function impairment.

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 withdrawn from the immunosuppressive regimen at 2-4 months post-transplantation, and Rapamune® dose was increased and adjusted to target trough whole blood 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.

On January 24, 2002, members of the subcommittee for immunosuppressants of the Antiviral Drugs Advisory Committee (ADAC) addressed the supplemental NDA and recommended that one identify the renal transplant population who would most benefit from concentration-controlled sirolimus with early cyclosporine withdrawal regimen as well as determine the minimum efficacious and maximal tolerated sirolimus concentrations and method of therapeutic drug monitoring (TDM).
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 both groups. However, the number of discontinuations appeard higher in the CsA withdrawal group.

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 Advisory Committee concerns and to complete all the post-marketing commitments established in the September15, 1999- initial approval letter for Rapamune® oral solution.

Wyeth filed a complete re-submission on October 11, 2002. Additionally, on January 31, 2003 the applicant submitted a major clinical amendment including a 3-years safety summary from study 310.

On April 11, 2003, FDA approved efficacy supplements S-006 (NDA 21-083) and S-004 (NDA 21-110) for both the oral solution and tablet formulations of Rapamune® that provided for cyclosporine withdrawal in patients at low to moderate risk for rejection. This new labeling received three years of marketing exclusivity, extending Wyeth's privileges until April 11, 2006.

In the present application, the limited data available in children was addressed by Wyeth:

- By studying the effects of the Sirolimus plus a calcineurin inhibitor (CInh) regimen versus standard therapy in high-risk pediatric renal transplant subjects with chronic allograft nephropathy and
- By collecting pharmacokinetic data from studies 217 and 315.

Reviewer's Comments: ***The long term chronic use of cyclosporine together with Rapamune® as a maintenance regimen is no longer considered to be an acceptable regimen in renal transplant recipients at low to moderate risk for rejection due to the resulting increase in renal impairment.***

5 OTHER CLINICAL EXPERIENCE WITH SIROLIMUS IN PEDIATRIC SUBJECTS

5.1 Pediatric Clinical Experience in Other Studies Conducted by Wyeth.

Table 4.1- 1.

PROTOCOL	*ALL PATIENTS ENROLLED*	*PEDIATRIC PATIENTS No (age)*	*TREATMENT ASSIGNMENT (No)*
0468E1-302-GL	576	3 *(< 18 yrs)*	*Sirolimus 2 mg/day, (1)* *Sirolimus 5 mg/day, (1)* *Placebo (1)*
0468E1-301-US	719	12 *(12 to 18 yrs)*	*Sirolimus 2 mg/day (6)* *Sirolimus 5 mg/day (3)* *Azathioprine (3)*

Protocol 0468E1-302-GL, Adverse events in the subjects receiving sirolimus included hyperlipidemia, anemia, elevated creatinine, and lymphocele.

Protocol 0468E1-301-US, Two (2) of the 9 subjects (22%) receiving sirolimus developed acute rejection; these occurred in the 2 mg/day group. No rejection episodes occurred in the group receiving azathioprine. No subjects died or experienced graft loss.

5.2 Other Relevant Clinical Experience with Sirolimus in Pediatric Renal Allograft Recipients

Table 5.2-1 represents a summary of the literature review provided by the applicant. It appears to support the findings in the Biopharmaceutical Review (Please see Biopharmaceutical Review)

Table 5.2-1

INVESTIGATOR	***PATIENTS ENROLLED (AGE IN YRS)***	***MAINTINANCE IMMUNOSUPPRESSIVE REGIMEN (No)***	***FOLLOW-UP***	***ADVERSE EVENTS***
Vilalta et al.[5]	***6 (2 to 18)***	***SRL[6], MMF[7], CS, and CsA*** (CsA was withdrawn 7 days after transplant)	12 months	Hyperlipidemia
El-Sabrout et.al.[8]	***20 (3-18)***	***SRL, FK506[9], CS***	12 months	Hyperlipidemia Lymphocele
Grimm et al[10]	***8 (7-17)***	***CsA, and CS.***	Pharmacokinetic Study	

Vilalta et al[5]:
All subjects were reported to have normal creatinine levels at 14 days and at 12 months after transplant. None experienced acute rejection during or after CsA withdrawal.
The clearance of sirolimus was found to be higher in the younger children, resulting in the need to prescribe doses that were 20% to 50% higher than those required to maintain comparable trough levels in the older subjects.

El-Sabrout et.al.[8]:
There were no reports of acute rejection episodes during the first year post transplant, and 1-year actuarial patient survival and graft survival rates were both100%.

Grimm et al[10]:
Thirteen (13) pharmacokinetic profiles were obtained in 8 stable pediatric renal allograft recipients (4 children and 4 adolescents)
These PK profiles were compared with those of 26 stable adult renal allograft recipients.
The mean oral clearance (CL/F) was higher, and the mean half life ($t_{1/2}$) was shorter in the 4 children when compared with the corresponding values for the adolescent and adult cohorts.

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[5] Vilalta R, Vila A, Nieto J, et al. Rapamycin use and rapid withdrawal of calcineurin inhibitors in pediatric renal transplantation. *Transpl Proc*. 2003;35:703-704.

[6] SRL = Sirolimus (Rapamune®)
[7] MMF= Mycophenolate mofetil (Cell Cept ®)
[8] El-Sabrout R, Weiss R, Butt F, et al. Rejection-free protocol using sirolimus-tacrolimus combination for pediatric renal transplant recipients. *Transpl Proc*. 2002;34:1942-1943.

[9] FK506= Tacrolimus
[10] Grimm EM, Kelly PA, Swinford RD, et al. Sirolimus pharmacokinetics in pediatric renal transplants. *Pediatr Transpl*. 2000;4:S86A (abstr, suppl 2).

In addition, a progressive increase in sirolimus whole blood concentrations was observed between 2 and 8 weeks Posttransplantation.

Reviewer's Comments:
Data from Grimm et al. suggest that younger children (4 to 10 years) may require higher doses of sirolimus than adolescents and adults to achieve similar drug exposure (Please see Clinical pharmacology review)

6 PEDIATRIC EXCLUSIVITY DETERMINATION - WRITTEN REQUEST ITEMS-

As recognized by the sponsor, "The limited amount of data available from previous studies underscores the need for additional data regarding sirolimus pharmacokinetics in pediatric subjects, particularly those under the age of 13 years."

To address the above concerns, NIH in collaboration with Wyeth and FDA, initiated study 0468E1-217-US. A full study report including safety and efficacy information was submitted for study 217. However this study ultimately contributed PK data on only 3 individuals.
In addition, the NIH was currently conducting ***study SW01*** in pediatric renal transplant recipients. PK data was obtained in a subset of 44 children from this study which is still ongoing, after the study was unblended (Wyeth ***protocol 0468H1-315-WW***).

6.1 Types of Studies and indications:

The agency requested:

- "An open label comparative study to evaluate the safety and efficacy of sirolimus versus the best local therapy on clinical outcomes and histologic progression of allografts nephropathy in high-risk pediatric renal transplant patients". and
- "The evaluation of the pharmacokinetic profiles of sirolimus in pediatric renal transplant recipients receiving Rapamune®."

The submission included two studies:

- ***Protocol No. 0468E1-217-US:*** ***"An Open-Label, Comparative Study of the Effect of Sirolimus versus Standard Treatment on Clinical Outcomes and Histologic Progression of Allograft Nephropathy in High Risk Pediatric Renal Transplant Patients,"***

Protocol 217 was a randomized, outpatient study in high-risk pediatric renal transplant subjects. Eligible subjects were those with ≥ 1 episode of acute rejection as well as those subjects with biopsy-proven chronic rejection. Because of enrollment difficulties, enrollment in the study was halted at 102 subjects.
Subjects were randomized in a 2:1 ratio to have sirolimus added to their calcineurin inhibitor regimen or to continue their current calcineurin inhibitor regimen.

Protocol 217 compared the safety and efficacy of sirolimus (SRL) + Cyclosporine (CsA) + corticosteroids (CS) or SRL + Tacrolimus (TAC) + CS versus standard therapy which includes double therapy (CsA or TAC + CS) or triple therapy which will also include azathioprine or MMF.

- ***Protocol No. 0468H1-315-US:*** ***"A Double-Blind Randomized Trial of Steroid Withdrawal in Sirolimus and Cyclosporine-Treated Primary Transplant Recipients."***

Protocol 315 was a randomized clinical trial in which corticosteroids were to be eliminated 6 months after transplant in a blinded fashion from an immunosuppressive regimen containing sirolimus and a calcineurin inhibitor in primary pediatric renal allograft recipients.
In addition to the characterization of the pharmacokinetics of sirolimus, the study compared steroid withdrawal, frequency and severity of rejection, and graft survival over 2 years, compared growth, lipid profile, and blood pressure at 1 and 2 years, and evaluated a method to prioritize patients for steroid withdrawal.

- ***Pharmacokinetic data was evaluated across two studies (Protocol No. 0468E1-217-US and Protocol No. 0468H1-315-US).***

Study 217 provided data for pharmacokinetic profiling from three (3) subjects.
Study 315 accounted for approximately 94% (44/47) of the PK data.
A report (RPT-55555) for the pharmacokinetic analysis of the combined data from the 2 protocols was included in this submission. (See Clinical Pharmacology review)

6.2 Age groups and number of patients studied:

"The agency requested a total of 18 pediatric renal transplant recipients to be studied for pharmacokinetics (pk) across the age groups of 0-5 years, 6-11 years, and 12-18 years *(6 evaluable patients per age group).*. An acceptable alternative was to study a total of 10 evaluable patients in the 0-11 year old age group, and 8 evaluable patients in the 12-18 year old age group for pk evaluation."

Protocol No. 0468E1-217-US: 102 patients were enrolled and analyzed for primary efficacy endpoint (intent-to-treat), n = 99 were analyzed for safety; and n = 98 were analyzed in an efficacy subpopulation.

Table 6.2-1 Protocol No. 0468E1-217-US: Age and treatment groups at study entry.

Years, n (%)	*Sirolimus*	*Per local practice: **	*Total*
0 to 5	4 (6)	1 (3)	5 (5)
6 to 11	20 (31)	4 (11)	24 (24)
12 to 17	29 (45)	20 (54)	49 (48)
≥ 18	12 (18)	12 (32)	24 (24)
Totals	65	37	***102***

* This consisted of double-drug therapy (CsA or tacrolimus + steroids) or triple-drug therapy (either CsA or tacrolimus + steroids + MMF or azathioprine)

Protocols 0468H1-315-US and 0468E1-217-US - Pharmacokinetics: 49 pediatric renal transplant recipients receiving sirolimus plus calcineurine based immunosuppressive regimens (Including CsA approved for use with SRL, and tacrolimus not approved for this combination) were enrolled in the sirolimus PK evaluation in both protocols. (SRL + CsA, n = 25; SRL + TRL, n = 24). From those, 47 patients were evaluated for PK across three age groups (See Table 6.2-2).

C_{max}, T_{max}, AUC, and CL/F were calculated for each patient and summarized by age group, and by treatment (sirolimus + CsA, sirolimus + tacrolimus, CsA alone, and tacrolimus alone). Pharmacokinetic analysis methods were described. Three subjects from Protocol 0468E1-217-US received treatment with SRL + CsA (n = 3), while 44 subjects from Protocol 0468H1-315-US received treatment regimens with SRL + CsA (n = 22) and SRL + TRL (n = 22).

Reviewer's Comments: ***The ideal goal of enrolling 6 evaluable subjects in each of 3 age groups (0 to 5 years, 6 to 11 years, and 12 to 18 years) was not achieved. The alternative enrollment per treatment arm was acceptable: SRL + CsA (0 to 11 years, n = 11; 12 to 18 years, n = 14) and SRL + TRL (0 to 11 years, n = 13; 12 to 18 years, n = 9).***

Table 6.2-2 Studies 0468E1-217-US and 0468H1-315-US
Age and treatment groups for pharmacokinetic evaluation.

Age groups	*Total*	SRL + CsA	SRL + TAC
0 to 5	*7*	3	4
6 to 11	*17*	8	9
12 to 17	*23*	14	9
Total	*47*	25	22

The three (3) subjects from Protocol No. 0468E1-217-US received treatment with SRL + CsA), while the 44 subjects from Protocol No. 0468H1-315-US received both treatments SRL + CsA (n = 22) and SRL + TRL (n = 22).

Reviewer's Comments:
The sponsor performed the type of studies on the indications requested by the agency; the number of pediatric patients enrolled in these studies was acceptable.

6.3 Clinical Endpoints:

Protocol No. 0468E1-217-US:
Efficacy was assessed by comparing the composite endpoint of biopsy-proven acute rejection, graft loss, or death after 36 months of treatment.

The requested objectives were defined. The efficacy and safety variables and outcomes were further described. Statistical methods including use of Kaplan-Meier and log rank methods were outlined.

Safety was assessed by comparing the composite endpoint of graft loss or death after 36 months of treatment

Protocol No. 0468H1-315-US and Protocol No. 0468E1-217-US:
Sampling time points appear to be adequate to determine the PK profile of orally administered sirolimus. Blood sampling was performed at multiple time points for PK analysis. A 24-hour pharmacokinetics flow chart for the Protocol No. 0468E1-217-US was included. A 24-hour pharmacokinetics flowchart for study 315-US was included.

6.4 Drug Specific Safety Concerns:

The Sponsor addressed drug-specific safety concerns as requested by the agency. Patients were monitored for the development of hypercholesterolemia, hypertriglyceridemia, elevated lactate dehydrogenase (LDH), hypophosphatemia, hypokalemia, reduction in platelet and WBC counts, epistaxis, headache, stomatitis, dyspepsia, anemia, arthralgia, and infections. Adverse event analyses were presented and reviewed. (Please see section 9 of this review for a more detailed presentation of the safety data)

6.5 Regimens, Dosage and Formulation:

Sirolimus was administered orally either as Oral Solution (1 mg/mL or 5 mg/mL) and/or Tablet (1 mg, 2 mg or 5 mg).
In Study 217, sirolimus was administered at a dose of 3 mg/m^2/day at 4 hours after the morning dose of either cyclosporine or tacrolimus. There after, sirolimus dose was adjusted to achieve trough whole blood sirolimus concentration in a range from 5 to15 ng/mL (chromatographic method).

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In Study 315, the starting daily dose was 6 mg/m^2 on postoperative day 1. At the investigator's discretion, the total daily sirolimus dose was given either at a single time or one-half the total daily dose was administered approximately every 12 hours and the sirolimus dose was adjusted to maintain sirolimus troughs within a target range from 10 to 20 ng/mL (chromatographic method).
(See section 7 of this review and the Biopharmaceutical Review for additional details)

6.6 Statistical Analyses:

The intent to treat population (ITT) n=102, was used for efficacy analyses (See section 8 of this review).
Table 6.6-1 Subject Evaluability.

Population subset	*Sirolimus*	*Standard*	*Total*
Enrolled	*65*	*37*	*102*
Intent to treat	*65*	*37*	*102*
Safety Analysis[11]	*64*	*35*	*99*
Efficacy Subpopulation[12]	*63*	*35*	*98*

[11] Received at least one dose of study medication.

Subgroups of the ITT population were used for safety analyses n=99 (patients receiving at least one dose of study medication) and efficacy analyses (all randomized patients who received at least 21 or more days of therapy). (See section 9 of this review).
The Cmax, Tmax, AUC, and CL/F of sirolimus were determined for each patient, and each age group, using non-compartmental methods. (See Section 7 of this review).

Reviewer's Comment: The sponsor fulfilled the request for characterizing PK profiles of sirolimus in children in the studied population.

6.7 Proposed Labeling:

The additional information from the pediatrics studies was proposed for the following sections:

- **CLINICAL STUDIES, Pediatrics**.
- **CLINICAL PHARMACOLOGY, Pharmacokinetics,** ***Special Populations***, Pediatric.
- **ADVERSE REACTIONS, Pediatrics** sections of the Rapamune labeling and
- Revisions to the **PRECAUTIONS, Pediatric Use** section.

(Please see the labeling revision section 11.1 of this review, page 24)

6.8 Format of Study Reports:

Full study reports including pharmacokinetic data, addressing the issues outlined in the request with full analysis, assessment, and interpretation were submitted.
A pharmacokinetic report containing full analysis, assessment and interpretation from the PK portions of the Protocol No. 0468E1-217-US and ongoing Protocol No. 0468H1-315-US study were also provided.
Race and ethnicity data are provided for all patients, with the exception of one subject for whom the requested information was not provided.

- ***The sponsor fulfilled this request.***

6.9 Date for Study Reports Submission:

The Waxman-Hatch exclusivity for Rapamune expired on September 15, 2004. Pediatric study reports were to be submitted to the Agency on or before December 31, 2004. This submission was received on September 13, 200, before the exclusivity expired, and a summary of the submission was presented before the Pediatric Exclusivity Board on November 17, 2004. The product was granted 6 months of additional exclusivity having met all of the requirements of the Pediatric Written Request.

[12] Received at least 21 days of study medication.

7 CLINICAL PHARMACOLOGY HUMAN - PHARMACOKINETICS & PHARMACODYNAMICS-

Protocols 0468E1-217-US and 0468H1-315-WW

(Please see clinical pharmacology review)

This submission contains results of the first pharmacokinetic studies in pediatric renal allograft subjects receiving Rapamune® reported to FDA. The sponsor has previously performed pharmacokinetic studies of Rapamune® in adults (healthy subjects, and in patients with renal allografts, liver allografts, psoriasis, and hepatic impairment). The only previous pediatric experience was limited to a small number of pediatric subjects with stable chronic renal failure undergoing dialysis.

The sponsor has presented a supportive literature review, providing additional evidence that weight normalized oral-dose clearances (CL/F/kg) for CsA, tacrolimus and sirolimus are approximately 2-fold greater in pediatric patients compared to adult patients.

In this submission, pediatric subjects enrolled in protocols 217 and 315 were to have sirolimus and CsA or tacrolimus administered by concentration control. The target ranges for whole blood sirolimus concentrations in these protocols were 5 to 15 ng/mL and 10 to 20 ng/mL, respectively (chromatographic method).
Forty-nine (49) pediatric renal transplant subjects were enrolled in the PK study. All subjects completed the study. Forty-seven (47) subjects were included in the pharmacokinetic analysis presented in this submission (Two outliers exhibited extremely uncharacteristic sirolimus concentration-time profiles and were excluded).

7.1 Sirolimus and CsA Regimen.

Table 7.1-1

	0 to 11	*12 to 18*	*p*
CsA Doses[13] (mg/kg)	5.98	4.15	0.0434
Sirolimus Doses[14] (mg/kg)	0.0708	0.0529	0.0386
C_{max} (ng/mL)	21.9	34.5	0.0083
CL/F (L/h/kg)	0.266	0.136	0.0101
CL/F (L/h/m^2)	6.67	4.71	ns
t_{max} (hrs)	5.00	2.71	ns
AUC_{0-24h} (ng•h/mL)	322	466	ns

- ***Children from 3 to 5 years old (n=3) appeared to have lower sirolimus (AUC_{ss}) exposure (57% & 60%) and higher sirolimus CL/F/WT (3-fold & 2.2-fold) compared to adolescents and adults, respectively. (Please see clinical pharmacology review). However, the number in this age group (n=3) may be too small and variability to great to draw definitive conclusions*** (b) (4)

[13] once-daily dose
[14] once-daily dose

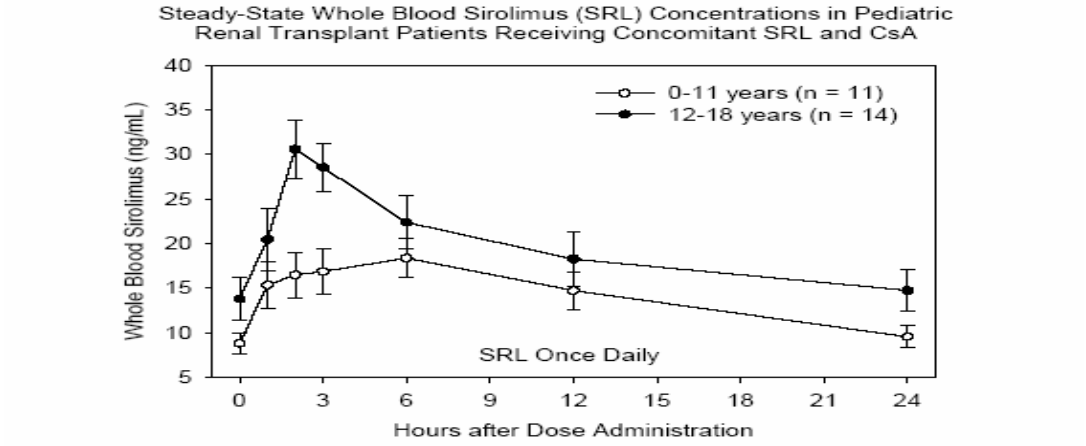
- ***Sirolimus once-daily doses in mg/kg were significantly higher among younger subjects (0 to 11 years) compared with older subjects (12 to 18 years). The mean sirolimus doses expressed in mg/m2 were similar in younger compared to older subjects (1.81 vs. 1.86 mg/m2).***
- ***CsA once-daily doses showed statistically significant differences between age groups when expressed in mg and mg/kg , but not in mg/m2.***

- ***Whole blood sirolimus C_{max} was significantly lower and CL/F was significantly higher in younger subjects compared with older subjects.***

Figure 7.1.-1 Steady-State Mean ± SE Whole Blood Sirolimus Concentrations in Pediatric Renal Transplant Patients Receiving Sirolimus and CsA

The applicant choose to group the cohort of patients aged up to 5 years old (n=3) with those aged 6-8 (n=8). Please See Biopharmaceutics review for analyses excluding the three youngest subjects from this group.

Figure 2.5.3.4.1.2-1: Steady-State Whole Blood Sirolimus Concentrations in Pediatric Renal Transplant Subjects Receiving Concomitant Sirolimus and CsA



- ***The figure 7.1-1shows that younger (0 to 11 years) subjects tended to have lower whole blood sirolimus concentrations than older (12 to 18 years) subjects.***

- ***Despite the significantly higher weight-normalized doses of sirolimus (mg/kg) and CsA in these younger subjects (See table 7.1-1), the tendency towards lower exposure in younger subjects persisted.***

7.2 Sirolimus and Tacrolimus Regimen.

Sirolimus and Tacrolimus Doses

- ***Sirolimus twice-daily doses in mg/kg were significantly higher in younger subjects (0 to 11 years) compared to older subjects (12 to 18 years)[15], but there were no significant differences between age groups for doses in mg or mg/m2.***
- ***Sirolimus once-daily doses showed only small non-significant differences in younger subjects compared with older subjects when***
- ***Tacrolimus twice-daily doses were not significantly different between age groups.***

(Please see the Biopharmaceutics review for a more detailed discussion of this regimen.)

7.3 Relationship between Sirolimus C_{min} and AUC

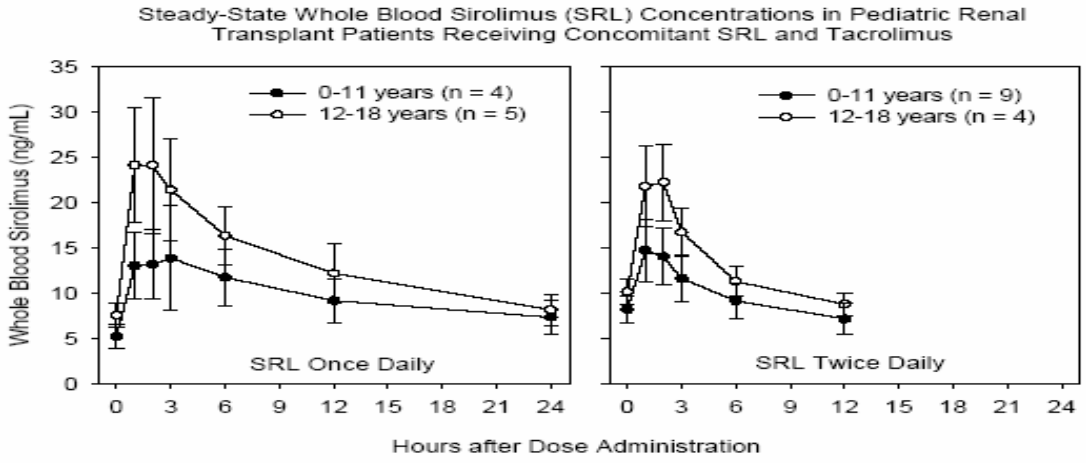
Ideally, AUC is associated with efficacy and safety. However, C min is a good enough surrogate for monitoring systemic sirolimus exposure, as it correlates well with AUC in adults.

The usefulness of $C_{min,ss}$ as a surrogate for AUC_{ss} in pediatric renal transplant subjects was investigated by linear regression analysis. The analyses showed strong correlations between $C_{min,\tau}$ and $AUC_{0-\tau}$ (τ = length of the dose interval) among all treatments and regimens.

7.4 Whole Blood Sirolimus Pharmacokinetic Parameters

Figure 7.4-1 Steady-State Mean ± SE Whole Blood Sirolimus Concentrations-time profiles in Pediatric Renal Transplant Patients Receiving Sirolimus with Tacrolimus.

Figure 2.5.3.4.2.2-1: Steady-State Whole Blood Sirolimus Concentrations in Pediatric Renal Transplant Subjects Receiving Concomitant Sirolimus and Tacrolimus



[15] Sirolimus Doses: *0 to 11* years: (0.0921mg/kg) versus *12 to 18years* (0.0492mg/kg); p=0.0261

Younger (0 to 11 years) subjects tended to have lower whole blood sirolimus concentrations than older (12 to 18 years) subjects after both sirolimus once- daily and twice daily administration. The ranges in whole blood sirolimus concentrations for once-daily and twice-daily administration were quite similar. (Please see Biopharmaceutics review for a more detailed discussion of the age groups 3-5 years old (n=3) and 6-11 years old (n=8)).

8 EFFICACY

The primary objective in study 0468E1-217-US was to compare the safety and efficacy of sirolimus (SRL) plus a Calcineurin Inhibitor (CsA or tacrolimus) and corticosteroids (CS) versus **"standard therapy"** in high-risk pediatric renal allograft recipients[16] .
Standard therapy included:

- Double therapy (CsA or TAC and CS) or
- Triple therapy (CsA or TAC plus azathioprine or MMF and CS)

(See section 1.4 Abbreviations and Definition for a more detail explanation of the regimens involved in this study).
The study intended to demonstrate superior efficacy of sirolimus when added to standard calcineurine inhibitor-based immunosuppressive therapy.

Efficacy was assessed by comparing the efficacy failure rate defined as the composite endpoint of the first occurrence of biopsy-proven acute rejection, graft loss, or death after 36 months of treatment. Efficacy failure in the intention-to-treat (ITT) population, n=102 was numerically more frequent in subjects randomly assigned to receive the combination of sirolimus and a calcineurin inhibitor than in the subjects allocated to standard therapy (44.6% versus 32.4%, respectively; p = 0.294).
In the subset of all subjects younger than 18 years, the efficacy failure rates were similar (45.3% and 44.0%, respectively; p = 1.000) (See table 8-1, below)
Kaplan-Meier (time-to-event) analyses of efficacy failure, for the overall ITT population (n= as well as the subset of subjects younger than 18 years, showed no statistically significant difference between cohorts.

[16] Eligible subjects were those with ≥ 1 episode of acute rejection as well as those subjects with biopsy-proven chronic rejection.

Table 8-1 Efficacy Failure Rates, ITT analyses at 36 months, study 217.

	All Ages		Age < 18 Years	
Rate, n (%)	***Sirolimus (n = 65)***	***Standard (n =37)***	***Sirolimus (n =53)***	***Standard (n = 25)***
Efficacy Failure	**29 (44.6)***	**12 (32.4)***	**24 (45.3)**	**11 (44.0)**
Biopsy-confirmed acute rejection	19 (29.2)	7 (18.9)	16 (30.2)	6 (24.0)
Graft loss	10 (15.4)	5 (13.5)	8 (15.1)	5 (20.0)
Death*	0	***0***	***0***	***0***

Differences in rates were not statistically significant for all the comparisons.
* 95% CI, (-7.1, 31.5), Fisher exact p-value = 0.294
* *2 subjects died, both had graft loss before they died, so they were counted under graft loss for the primary endpoint. Abbreviations: ITT = intent-to-treat; CI = confidence interval.
Source: data obtained from the sponsor's application CSR-52810, protocol 0468E1-217-US, Tables 9.4.1-1 and 9.4.1-2 page 82

Source: Table obtained from the sponsor's application CSR-52810, protocol 0468E1-217-US, page 82.

Reviewer's Comment: ***These results do not support that the addition of sirolimus to a standard immunosuppressive regimen of calcineurin inhibitor plus corticosteroids provides superior clinical benefit in pediatric renal transplant recipients as high risk for rejection.***

9 SAFETY

Study 0468E1-217-US was not powered to make comparisons with respect to graft loss or patient death; however, these were evaluated for safety purposes by comparing the composite endpoint of graft loss or death after 36 months of treatment.
The cumulative rate of graft loss at month 36 was numerically higher (p = 0.327) in the sirolimus cohort (17/65, 26.2%) than in the standard therapy cohort (6/37, 16.2%). Two (2) deaths were reported during the study, 1 in each randomized cohort, both had graft loss before they died, so they were counted under graft loss.

Table 9-1 Rate of Graft Loss at 36 months: ITT, study 217.

	All Ages		Age < 18 Years	
Rate, n (%)	***Sirolimus (n = 65)***	***Standard (n =37)***	***Sirolimus (n =53)***	***Standard (n = 25)***
Graft loss	***17 (26.2)****	***6 (16.2)****	***14 (26.4)****	***5 (20.0)****
Death*	0	***0***	***0***	***0***

2 subjects died, both had graft loss before they died, so they are counted under graft loss for the primary endpoint graft loss or death.
*Fisher exact p-value 0.327, $(95\% CI)_c$ (-6.0, 25.9)

**Fisher exact p-value = 0.587, (95% CI)c (-13.3, 26.1)

Safety was also assed analyzing the AE reports. The cumulative frequency of adverse events (AEs) in the ITT analysis was numerically similar in sirolimus plus a CInh group (76.9%) versus a CInh without sirolimus (73%). The types of events were consistent with the known safety profile of sirolimus.

9.1 Adverse Events

Among AEs reported at a cumulative frequency of 10% or greater, abdominal pain, fever, abnormal renal function, and urinary tract infection were significantly more common in the sirolimus treatment group compared with standard therapy. (See table below)

Table 10.2-1: Number (%) of Subjects Reporting Adverse Events at a Frequency ≥ 10% in Either Treatment Group (36-Month Data)

Body System Adverse Event	Sirolimus (n = 65)	Standard (n = 37)	Total (n = 102)	Fisher's Exact p-Value[a]
Any adverse event (1 or more)	50 (76.9)	27 (73.0)	77 (75.5)	0.81
Body as a whole				
Abdominal pain	12 (18.5)	1 (2.7)	13 (12.7)	0.029*
Fever	12 (18.5)	1 (2.7)	13 (12.7)	0.029*
Infection	10 (15.4)	3 (8.1)	13 (12.7)	0.37
Surgical treatment	4 (6.2)	4 (10.8)	8 (7.8)	0.46
Cardiovascular system				
Hypertension	13 (20.0)	6(16.2)	19 (18.6)	0.79
Digestive system				
Diarrhea	9 (13.8)	4 (10.8)	13 (12.7)	0.765
Hemic and lymphatic system				
Anemia	12 (18.5)	7 (18.9)	19 (18.6)	1.0
Metabolic and nutritional				
Creatinine increased	11 (16.9)	3 (8.1)	14 (13.7)	0.25
Nervous system				
Headache	12 (18.5)	3 (8.1)	15 (14.7)	0.24
Respiratory system				
Pharyngitis	8 (12.3)	1 (2.7)	9 (8.8)	0.15
Rhinitis	8 (12.3)	2 (5.4)	10 (9.8)	0.321
Respiratory disorder	7 (10.8)	3 (8.1)	10 (9.8)	0.74
Sinusitis	6 (9.2)	5 (13.5)	11 (10.8)	0.522
Urogenital system				
Kidney function abnormal	7 (10.8)	0	7 (6.9)	0.046
Urinary tract infection	15 (23.1)	1 (2.7)	16 (15.7)	0.009*

a. *p < 0.05
Source: EMMES 08 June 2004 and CDR 5-5-10PCT

Source: Wyeth'S application. Study-217-us-csr-52810.pdf , page 126.

Reviewer's comment: ***These results include a small number of subjects who were greater than 17 years old (up to 21 years old). In addition "standard therapy" represented a variety of regimens preferred at each study site (See section 1.4 Abbreviations and definitions of this review)***

Among the AEs reported at cumulative rates below 10%, pneumonia and stomatitis were numerically but not significantly more common among sirolimus-treated subjects.

9.2 Relevant Drug Related Adverse Events:

- **Stomatitis**. The development of lesions involving the oral mucosae—variably reported as "aphthous stomatitis," "mouth ulceration," or "oral lesion"—was observed in 4 sirolimus-treated subjects, for a cumulative gross frequency 6.3%
- **Gingival hyperplasia**, a known consequence of CNI therapy, was reported for 4 subjects randomly assigned to sirolimus, and 1 to standard therapy (6.2% and 2.7%, respectively).
- **Hyperlipidemia** (hypercholesterolemia and/or hypertriglyceridemia) was reported in 7 (10.8%) sirolimus-treated and 1 (2.7%) standard therapy subjects.

9.3 Life Threatening Adverse Events:

Seven Adverse events (AE's) were considered life threatening (malignancy n = 2, sepsis n = 1, pneumonia/sepsis n = 1, drug overdose n = 1, encephalitis n = 1, and postrenal biopsy hemorrhage n = 1. Two of those resulted in deaths. (See table below)

Table 10.3.1.1-1: Summary of Deaths That Occurred in the First 36 Months of Study

Therapy Group Subject Number (age, y)	Days of Therapy	Study Day of Death	Reason for Discontinuation of Study Drug	Cause of Death
Sirolimus (n = 1)				
JEBE3598 (5)	224	249	Rejection	Septicemia
Standard (n = 1)				
STCL9617 (14)	157	157	Graft failure	Cerebrovascular accident

Source: Source: Wyeth's application. Study-217-us-csr-52810.pdf , page 132.

Reviewer's Comments:

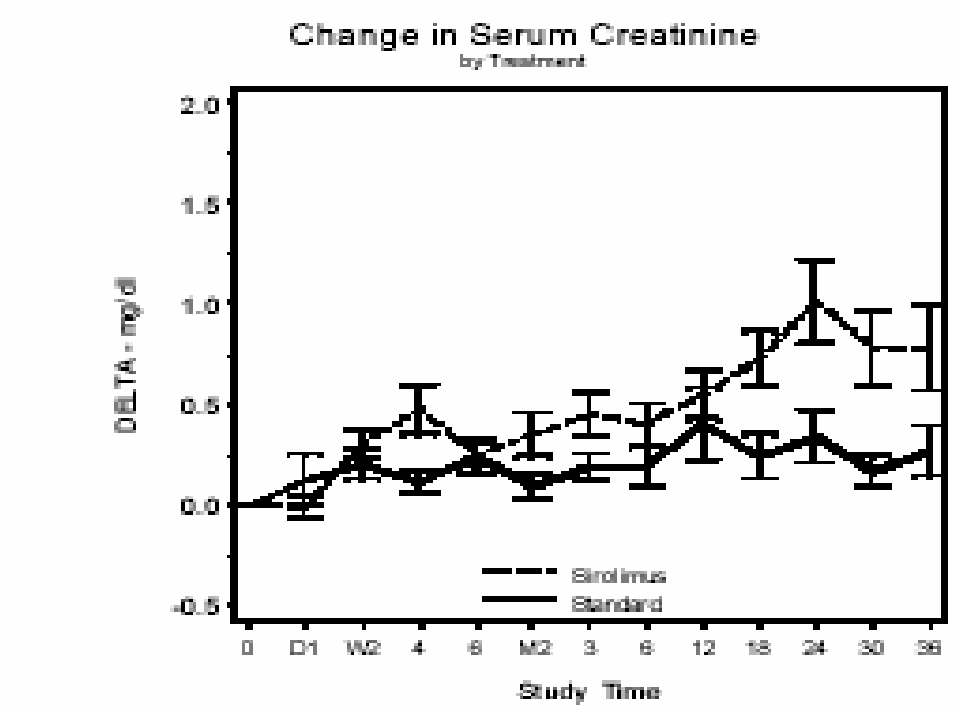
The open-label design of this trial makes difficult to analyze this results since the investigators AE's reports may be biased by knowing the treatment the patients were receiving. Taking this into consideration we observed a numerically higher incidence of certain adverse events (AE's), associated with the use of sirolimus in adults, in children treated with the sirolimus plus CInh combination versus standard therapy with CInh. The limited size of the study allows one, at best, to conclude that AE's associated with the use of sirolimus in adults were also observed in children. The study was too small to identify or exclude rare potential AE's specific to children that might not have been identified in adults.

9.4 Renal Function:

Adverse events denoting creatinine increase were numerically higher in the sirolimus + CInh combination 11(17%) versus the CInh alone 3(8%)

Serum creatinine concentration values did not differ statistically between treatments groups. However, these results should be interpreted with caution because of the size of the study is small to reliably exclude an effect of Sirolimus on cyclosporine induced nephrotoxicity. Furthermore, the mean serum creatinine mean changes from baseline values were significantly higher in subject randomly assigned to the sirolimus plus CInh combination compared to the CInh alone.

Figure 9.4-1 Mean (± SEM) Serum Creatinine Change from baseline overtime by treatment group

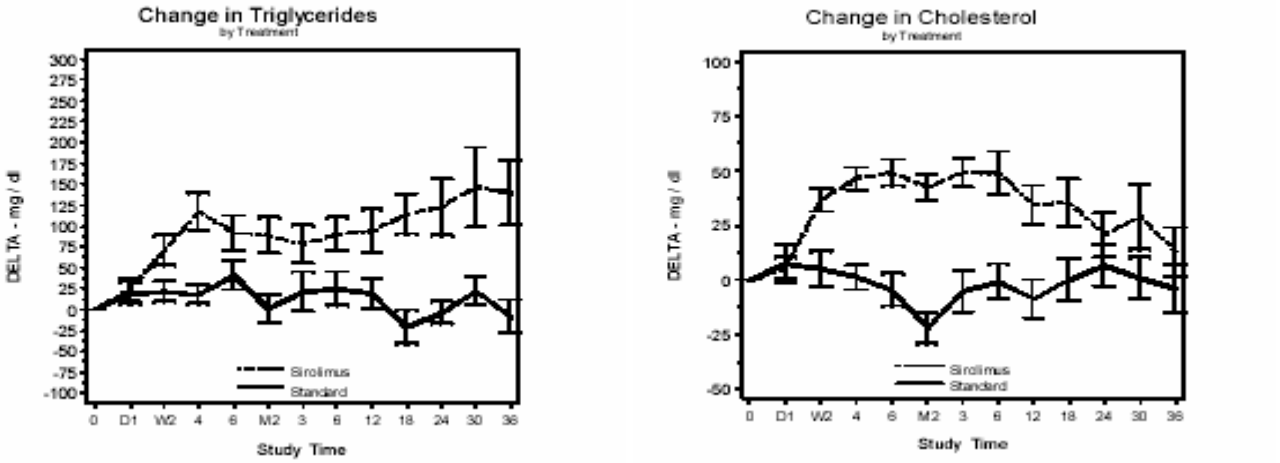


Source: Figure 10.4.1.1.2-1: Mean (± SEM) Change from Baseline Overtime by Treatment**.** From Wyeth's application. Study-217-us-csr-52810.pdf, page 147.

Reviewer's Comments: ***Renal function and data on related AE's results are consistent with the well known interaction between sirolimus and calcineurin inhibitor (CsA) therapy. In this study, renal function deterioration over time was significantly higher in subject randomly assigned to the sirolimus plus CInh combination compared to the CInh alone.(See figure 9-1 above)***

9.5 Serum Lipids:

Figure 9.4-1 Mean (± SEM) Serum cholesterol and triglyceride Change from baseline overtime by treatment group



Source: Figure 10.4.1.1.3-1 and 10.4.1.1.3-2: Mean (± SEM) Triglycerides levels and cholesterol Changes From Baseline Overtime by Treatment. Wyeth's application. Study-217-us-csr-52810.pdf, pages 151 and 152.

The mean changes from baseline in serum cholesterol and triglyceride levels were significantly higher among sirolimus treated group compared to the CInh alone group.

Reviewer's Comments: ***Data in children on hyperlipidemia reported as AE's and laboratory data on serum cholesterol and triglycerides are consistent with the well known toxicological profile of sirolimus in adults.***
The mean changes from baseline in serum cholesterol and triglyceride values were significantly higher over time among sirolimus plus CInh treated group compared to the CInh alone group. (See figure 9.5-1 above). These observations confirm that the types of

dyslipidemias, observed with the use of sirolimus in combination with calcineurin inhibitors in adults, were also observed in children.

10 CONCLUSIONS:

The subjects who participated in this study had previously experienced at least 1 prior episode of acute rejection or had histological evidence of chronic allograft nephropathy (chronic rejection) or both, and as a group, had reduced renal function at the time of enrollment[17].

This is consistent with the observation that, chronic rejection was the most common cause of graft loss for both treatment cohorts.

We agree with the sponsor that treatment of subjects with a prior history of acute rejection and/or chronic allograft nephropathy with the combination of sirolimus and a calcineurin inhibitor does not confer greater protection against recurrent acute rejection or progression of chronic allograft nephropathy than calcineurin inhibitor-based immunosuppression alone. Similarly, the addition of sirolimus to calcineurin inhibitor-based immunosuppression regimen did not reduce the risk of graft failure in the high-risk pediatric population studied and increased the risk for hyperlipidemia and faster renal function deterioration.

Lastly, among the renal transplant population, the overall safety profile of sirolimus in children and adolescents appears to be similar to that of adults, although the study was to small to permit detection or identify rare adverse events that may be specifically associated with the use of sirolimus in children.

Sirolimus Pharmacokinetics for Concomitant Sirolimus and CsA Therapy

Children from 2 to 5 years old had lower sirolimus (AUC_{ss}) exposure (57% & 60%) and higher sirolimus CL/F/WT (3-fold & 2.2-fold) compared to adolescents and adults, respectively. (Please see clinical pharmacology review)

Sirolimus and CsA once-daily doses in mg were significantly lower and doses in mg/kg were significantly higher among younger subjects (0 to 11 years) compared with older subjects (12 to 18 years).
Younger (0 to 11 years) subjects tended to have lower whole blood sirolimus concentrations than older (12 to 18 years) subjects, despite significantly higher weight-normalized doses of sirolimus and CsA in these subjects. Weight-normalized CL/F (L/h/kg) was significantly higher in younger subjects (0 to 11 years) compared with older subjects.

Sirolimus Pharmacokinetics for Concomitant Sirolimus and Tacrolimus Therapy

Sirolimus once-daily doses were not significantly different between age groups for any unitized sirolimus dose.

[17] This group of renal transplant recipient was defined as "high risk"

Sirolimus twice-daily doses in mg/kg were significantly higher in younger subjects compared to older subjects.
Younger (0 to 11 years) subjects tended to have lower whole blood sirolimus concentrations than older (12 to 18 years) subjects after both sirolimus once-daily and twice-daily administration.

Relationship between Sirolimus C_{min} and AUC
A strong correlation was observed between steady-state whole blood sirolimus C_{min} and AUC. These results indicate that sirolimus trough concentrations are adequate surrogates for sirolimus exposure.

Comparison of Sirolimus Pharmacokinetics among Pediatric and Adult Renal Transplant Subjects during Concomitant Sirolimus and CsA Therapy

Younger pediatric subjects (0 to 11 years) showed large increases compared to adult subjects (32 to 62 years) in dose normalized C_{max} (+116%, 32.4 vs. 15.0 ng/mL), dose-normalized AUC_{0-24h} (+104%, 470 vs. 230 ng•h/mL), and CL/F/kg (+91.4%, 0.266 vs. 0.139 L/h/kg).

These results suggest that younger pediatric renal transplant patients (0 to 11 years) require larger weight-normalized doses to achieve whole blood sirolimus concentrations comparable to those in adult renal transplant patients.
(Please see clinical pharmacology review for further details in the PK data analysis).

11 LABELING CHANGES

The Applicant proposed labeling changes in the **CLINICAL STUDIES/Pediatrics** section, **CLINCAL PHARMACOLOGY Pharmacokinetics,** ***Special Populations***, ***Pediatric:*** section, **ADVERSE REACTIONS, Pediatrics** section and, the **PRECAUTIONS, Pediatric Use** section, reflecting the new information obtained in children. These changes were discussed with the Applicant. Additional changes to the **INDICATIONS,** and **DOSAGE AND AMINISTRATION/Dosage Adjustments** section were also discussed. The revised labeling changes, which were agreed to with the Applicant during a Telephone Conference on March 9, 2005, and included in a revised package insert submitted on March 11, 2005, are listed below.

New **CLINICAL STUDIES/ Pediatrics** section:

> **Pediatrics:** Rapamune® was evaluated in a 36-month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric (aged 3 to <18years) renal transplant recipients considered to be at high immunologic risk for developing chronic allograft nephropathy, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Seventy-eight (78) subjects were randomized in a 2:1 ratio to Rapamune® (sirolimus target concentrations of 5 to 15 ng/mL, by chromatographic assay, n = 53) in combination with a calcineurin inhibitor and corticosteroids or to continue calcineurin-inhibitor-based immunosuppressive therapy (n = 25). The primary endpoint of the study was efficacy failure as defined by the first occurrence of biopsy confirmed acute rejection, graft loss,

or death, and the trial was designed to show superiority of Rapamune® added to a calcineurin-inhibitor-based immunosuppressive regimen compared to a calcineurin-inhibitor-based regimen. The cumulative incidence of efficacy failure up to 36 months was 45.3% in the Rapamune® group compared to 44.0% in the control group, and did not show superiority. There was one death in each group. The use of Rapamune® in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including but not limited to increased serum triglycerides and cholesterol) and urinary tract infections. This study does not support the addition of Rapamune® to calcineurin-inhibitor-based immunosuppressive therapy in this subpopulation of pediatric renal transplant patients.

New **INDICATIONS AND USAGE** section:

INDICATIONS AND USAGE
Rapamune® (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. It is recommended that Rapamune® be used initially in a regimen with cyclosporine and corticosteroids. 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 (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**).

The safety and efficacy of Rapamune® has not been established in pediatric patients less than 13 years old, or in pediatric (<18 years) renal transplant recipients considered at high immunologic risk (See **PRECAUTIONS, Pediatric use**, and **CLINICAL STUDIES, Pediatrics**).

New **PRECAUTIONS/ Pediatric Use** section:

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

The safety and efficacy of Rapamune® Oral Solution and Rapamune® Tablets have been established in children aged 13 or older judged to be at low to moderate immunological risk. Use of Rapamune® Oral Solution and Rapamune® Tablets in this subpopulation of children aged 13 or older is supported by evidence from adequate and well-controlled trials of Rapamune® Oral Solution in adults with additional pharmacokinetic data in pediatric renal transplantation recipients (See **CLINICAL PHARMACOLOGY, Special Populations, Pediatric**).

> Safety and efficacy information from a controlled clinical trial in pediatric and adolescent (<18 years of age) renal transplant recipients judged to be at high immunologic risk, defined as a history of one or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Rapamune® Oral Solution or Tablets in combination with calcineurin inhibitors and corticosteroids, due to the increased risk of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens, without increased benefit with respect to acute rejection, graft survival, or patient survival (See **CLINICAL STUDIES, Pediatrics**).

New **ADVERSE REACTIONS/ Pediatrics** section:

> **Pediatrics:** Safety was assessed in the controlled clinical trial in pediatric (< 18 years of age) renal transplant patients considered high immunologic risk, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy (see **CLINICAL STUDIES**). The use of Rapamune® in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including but not limited to increased serum triglycerides and cholesterol), and urinary tract infections.

For new changes to the sections on **CLINICAL PHARMACOLOGY/Special Populations/Pediatric,** and on **DOSAGE AND ADMINISTRATION/Dosage Adjustments,** please see the Biopharmaceutics Review.

Reviewer's Comment: ***These changes are acceptable and should be approved. The DOSAGE AND ADMINISTRATION/Dosage Adjustments section still states "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." This wording was included in the original label and was empirically derived to minimize the risk of potential over-dosage in very small individuals.*** (b) (4) [redacted]

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Concurrences:

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Medical Team Leader, DSPIDP

_____

Renata Albrecht, M.D.

Division Director, DSPIDP

cc: Division File

HFD-590/MO/AHernandez
HFD-590/MTL/MCavailleColl
HFD-590/Chem/MSeggel
HFD-590/Pharm/SKunder
HFD-590/Micro/ SBala
HFD-590/Biopharm/PColangelo
HFD-590/CPMS/RSaville

Concurrence Only:
HFD-590/Division Director /RAlbrecht

DFS Keywords
Admin: review

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Arturo Hernandez
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