Rapamune®(sirolimus) Maintenance Regimen

Summary for Presentation to

The Subcommittee of the Antiviral Drugs Advisory Committee on Immunosuppressive Drugs

Wyeth-Ayerst Research

24 January 2002

TABLE OF CONTENTS **Page**

TABLE OF CONTENTS **Page**

TABLE OF CONTENTS **Page**

1 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ALT	alanine aminotransferase [serum glutamic pyruvic transaminase]
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase [serum glutamic oxaloacetic transaminase]
ATG	antithymocyte globulin
ATN	acute tubular necrosis
$AUC_{0-\infty}$	total area under the concentration curve after a single dose
AUC_{0-24}	area under the concentration curve during a 24-hour dose interval
AUC_{0-t}	area under the concentration curve from time zero to time t
AUD_{0-t}	area under the dose curve from time zero to time t
AV	atrioventricular
AZA	azathioprine
BUN	blood urea nitrogen
B/P	whole blood to plasma ratio
CADI	chronic allograft damage index
CAN	chronic allograft nephropathy
CI	confidence interval
$C_{min,TN}$	time-normalized average steady-state trough whole blood concentration
$C_{min,24h}$	trough concentration during a 24-hour interval
CL/F	apparent oral-dose clearance
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CsA	cyclosporine (cyclosporin A)
CSR	clinical study report
CYP3A4	cytochrome P450 isozyme 3A4
DGF	delayed graft function
DN-$C_{min,TN}$	dose-normalized average trough whole blood concentration
$Dose_{TN}$	average time-normalized dose
EBV	Epstein-Barr virus
F	systemic availability
FDA	Food and Drug Administration
FK506	tacrolimus
FKBP	FK binding protein
GFR	glomerular filtration rate
GL	global
HDL	high-density lipoprotein
HPLC	high performance liquid chromatography
HUS	hemolytic uremic syndrome
ICH	International Conference on Harmonisation

Abbreviation	Definition
IL	interleukin
IMx	instrumentation by Abbott Laboratories for detection of sirolimus by microparticle enzyme immunoassay
IND	investigational new drug
ITT	intent-to-treat
LD	loading dose
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
MD	maintenance dose
MMF	mycophenolate mofetil
mRNA	messenger RNA
MS/MS	tandem mass spectrometry
mTOR	mammalian target of rapamycin
PD	pharmacodynamic
PK	pharmacokinetic
PTLD	posttransplant lymphoproliferative disease
RAPA	Rapamune
RMR	Rapamune maintenance regimen
SD	standard deviation
SEM	standard error of the mean
sNDA	supplemental New Drug Application
SRL	sirolimus
TDM	therapeutic drug monitoring
TEAE	treatment-emergent adverse event
UK	United Kingdom
UTI	urinary tract infection
UV	ultraviolet
V_{ss}/F	apparent oral-dose steady-state volume of distribution
VFE	valid-for-efficacy
W-AR	Wyeth-Ayerst Research
WBC	white blood cell

2 EXECUTIVE SUMMARY

The information presented here summarizes data submitted in the original supplemental New Drug Application (sNDA) as well as data submitted in subsequent correspondence with the Food and Drug Administration (FDA).

2.1 Proposed Indication

Rapamune® 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 (CsA) and corticosteroids. Cyclosporine withdrawal should be considered 2 to 4 months after transplantation.

2.2 Mechanism of Action

Sirolimus (rapamycin, Rapamune) is a novel macrocyclic lactone isolated from *Streptomyces hygroscopicus*. Sirolimus has a novel immunosuppressive biochemical mechanism of action, distinct from that of the calcineurin inhibitors (CsA and tacrolimus [FK506]) and the anti-metabolites (mycophenolate mofetil and azathioprine).

Sirolimus binds to the same immunophilin as tacrolimus (FK binding protein-12 [FKBP-12]). The sirolimus-FKBP complex does not affect calcineurin activity, unlike what occurs with CsA and tacrolimus. Rather, this complex binds to and inhibits the activation of a kinase called the mammalian target of rapamycin (mTOR). Inhibition of mTOR by sirolimus suppresses alloantigen- and cytokine-driven T-cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle.

Further in vitro studies have demonstrated that sirolimus inhibits cytokine- and growth factor-driven proliferation of B lymphocytes, as well as vascular and bronchial smooth muscle cells; these pathways are generally resistant to inhibition by the calcineurin inhibitors.

2.3 Key Results From CsA Elimination Clinical Trials

The results of the supportive CsA-elimination study 0468E1-212-GL (study 212) were consistent with the pivotal CsA-elimination study 0468H1-310-GL (study 310), and showed the following:

- In both groups, patient and graft survival were excellent; equivalent in study 310 and comparable in study 212.

- The 12-month acute rejection rates in the CsA-elimination arms were ≤ 22%. Acute rejection rates in the CsA-elimination arms were slightly (but not significantly) higher than those in the groups that received standard-dose CsA. There were no differences in the severity of the rejection episodes between the 2 groups.

- Renal function (calculated glomerular filtration rate [GFR]) at 6 and 12 months was significantly better in patients in the CsA-elimination arms.

- In those patients receiving concentration-controlled sirolimus (the CsA-elimination arms), rates of CsA-related treatment-emergent adverse events (TEAEs) were significantly lower than those in patients who received a fixed dose of sirolimus and a standard dose of CsA. These TEAEs included hypertension in both studies, increased creatinine values, hyperuricemia, and CsA toxicity in study 310 and hypomagnesemia, dyspnea, and edema in study 212.

- Patients in the CsA-elimination arms had higher rates of thrombocytopenia, hypokalemia, and liver function test abnormalities, possibly related to their greater sirolimus exposure.

- Lipid values were similar in both groups, despite higher sirolimus concentrations in the CsA-elimination arms.

- Patients in the CsA-elimination arm had significantly lower systolic and diastolic blood pressure at months 6 and 12 in study 310.

- Rates and types of infections were similar in both groups.

- Based on pharmacokinetic and pharmacodynamic analyses, a therapeutic window of 15 to 25 ng/mL (immunoassay) is suggested for concentration-controlled sirolimus, when used without CsA.

2.4 Key Results From Supportive Clinical Trials

2.4.1 Sirolimus Base Therapy Studies

The results of studies 207 and 210 showed the following:

- Patients receiving the Rapamune-based regimen had better renal function (lower mean serum creatinine values and higher mean calculated GFR values) than patients receiving the CsA-based regimen after both 1 year and 2 years of treatment.

- Patients receiving Rapamune-based and CsA-based regimens had similar rates of acute rejection, patient survival, and graft survival.

- The Rapamune-based regimen was associated with a lower incidence of the following investigator-reported events: increased creatinine values, tremor, and hypertension.

- The Rapamune-based regimen was associated with a higher incidence of hyperlipidemia and thrombocytopenia.

- No malignancies occurred in patients treated with Rapamune.

3 INTRODUCTION

The rate of acute rejection of transplanted cadaveric kidneys has been steadily decreasing, in part because of the increasing prevalence of multiple drug prophylactic regimens. Until recently, however, overall actuarial survival of transplanted kidneys remained unaffected, perhaps in part because of reliance on the chronic administration of CsA as the cornerstone immunosuppressant for most patients. The dose-dependent acute and chronic nephrotoxic effects of CsA are well described in the literature. CsA has been shown to increase the production of profibrotic cytokines and is postulated to have a direct pathogenic role in chronic allograft nephropathy. The prevalent practice of chronic CsA administration may contribute to the limited prognosis of transplanted organs by further compounding the cumulative damage of cold ischemia and acute and chronic antiallogeneic immunologic processes.

Both the therapeutic effect and nephrotoxicity of CsA are related to the inhibition of calcineurin. Thus, a potent immunosuppressive without calcineurin-antagonist properties that could limit the dose and duration of CsA exposure might prolong the half-life of transplanted organs and improve allograft function at all intermediate time points.

Sirolimus (rapamycin, Rapamune) was originally isolated in a discovery program for novel antifungal agents. It is a macrocyclic lactone fermentation product of *Streptomyces hygroscopicus*, an actinomycete that was isolated from a soil sample collected from Rapa Nui, commonly known as Easter Island.[1,2,3] Interest in sirolimus as an immunosuppressive agent results from its distinct mechanism of action and its efficacy in sustaining allograft survival.[4,5,6,7]

The mechanism of action of sirolimus is distinct from that of other immunosuppressive drugs.[8] The activity of macrocyclic immunosuppressive agents such as sirolimus, CsA, and tacrolimus (Prograf, FK506) depends on their binding to specific cytosolic binding proteins called immunophilins. The complex of CsA or tacrolimus with their respective immunophilins, cyclophilin and FKBP-12 respectively, inhibits calcineurin, a Ca^{2+}/calmodulin-dependent serine/threonine phosphatase required for the production of cytokines and early activation of T cells (G_0 to G_1).[9,10,11,12] The sirolimus-FKBP complex has no effect on calcineurin activity, but rather binds to mTOR (mammalian target of rapamycin). Inhibition of mTOR's critical kinase activity suppresses interleukin (IL)-2- and IL-4-driven T-cell proliferation, thus inhibiting progression of cells from the G_1 to the S phase of the cell cycle.[13] Furthermore, sirolimus-FKBP binding to mTOR inhibits translation of a family of messenger RNAs (mRNAs) that code for proteins essential for cell cycle progression.[14,15,16,17] In addition, sirolimus inhibits the IL-2-

induced transcription of proliferating cell nuclear antigen that is essential for DNA replication.[18] It also blocks CD28-mediated sustained up-regulation of IL-2 transcription in T cells.[19] Sirolimus reduces the kinase activity of the cdk4-cyclin D and cdk2-cyclin E complexes, resulting in decreased synthesis of cell cycle proteins cdc2 and cyclin A.[20]

In summary, sirolimus blocks the progression of the cell cycle from G_1 to S phase by inhibiting several signal transduction pathways. Its immunosuppressive mechanism of action is distinct from that of CsA, tacrolimus, and other immunosuppressive drugs such as mycophenolate mofetil (CellCept) and azathioprine. Its activity is not limited to normal cells of the immune system. It also inhibits proliferation of transformed cell lines of lymphoid, central nervous system, hepatic, melanocytic, osteoblastic, myogenic, renal, and connective tissue origin, as well as the proliferation of T and B cells transformed by human T lymphotropic virus I and Epstein-Barr virus, respectively.[21] Because sirolimus has a distinct mechanism of action, it can be administered with CsA to provide enhanced immunosuppression for patients undergoing solid organ transplantation.

Furthermore, there is no evidence that sirolimus increases blood pressure, a co-morbid condition that may lead to shortened graft survival and cardiovascular morbidity. Thus, it would seem that immunoprophylaxis with sirolimus-based therapy may lead to better renal function and potentially longer graft survival than is observed with traditional immunosuppressive therapy.

The first randomized clinical trial of sirolimus in renal transplantation (study 0468E1-203-GL[22]) examined its efficacy and safety when associated with full and reduced doses of CsA. This trial was the basis of the double-blind pivotal studies (0468E1-301-US[23] and 0468E1-302-GL[24]), which in turn were the basis of initial marketing applications throughout the world. Sirolimus was well tolerated and had a safety profile distinct from that of CsA. Rates of biopsy-confirmed acute rejection were reduced by the combination of a sirolimus dose of 1 or 3 mg/m^2 daily with full- or reduced-dose CsA and steroid, with no adverse impact on graft loss or death.

Concentration-controlled sirolimus- and CsA-based therapies were contrasted in 2 additional phase 2 renal transplant trials (0468E1-207-EU[25] and 0468E1-210-EU[26]). The results showed significantly lower serum creatinine concentrations (through 2 years after transplantation) among sirolimus-treated patients, with no significant difference in rates of acute rejection, graft loss, or death. Furthermore, sirolimus provided prophylaxis of acute rejection episodes beyond the immediate posttransplant period when administered without concomitant CsA.

The lowest acute rejection rates were obtained when sirolimus was coadministered with CsA, whereas an improved safety profile could be realized when CsA exposure was minimized or eliminated. This suggested that regimens combining sirolimus with CsA in the early posttransplant period, followed by dosage reduction and elimination of CsA, were the next logical step. As a result, 2 studies, 0468H1-310-GL (tablet formulation) and 0468E1-212-GL (oral solution), were initiated.

Study 310 and study 212 were designed to assess whether a combination therapy of CsA, corticosteroids, and sirolimus for the first 3 or 2 months, respectively, after transplantation followed by CsA elimination would result in low acute rejection rates and freedom from long-term CsA toxicities, notably hypertension and nephrotoxicity. These studies tested the concepts of early CsA withdrawal and of increasing the dosage of sirolimus to achieve and maintain whole blood trough concentrations (measured by immunoassay) in the range of 20 to 30 ng/mL (16 to 24 ng/mL, chromatographic) in study 310 or 10 to 20 ng/mL (8 to 16 ng/mL, chromatographic) in study 212, in order to offset the elimination of CsA from therapy.

4 TABLE OF STUDIES

The sNDA for Rapamune maintenance regimen (RMR) was submitted on 06 Apr 2001. The table of studies is provided in section 11. It gives the protocol number, the countries in which the study was conducted, report number, a brief description of the design of each clinical study, and the number of patients enrolled.

The studies are listed in the following order:

- Pivotal RMR study (non-IND).
- Supportive RMR study.
- Supportive base therapy (sirolimus versus CsA) studies.

5 DESIGN OF CLINICAL STUDIES

5.1 Pivotal RMR Study (Protocol 0468H1-310-GL)

Study 310 was designed to primarily assess the equivalence in the rates of graft survival at 12 months after transplantation in recipients of primary or secondary renal allografts who were receiving either continuous therapy with CsA and Rapamune (group A) or were receiving a regimen of CsA and Rapamune followed by concentration-controlled sirolimus and CsA elimination (group B). Secondary objectives included the incidence of acute rejection at 6 and 12 months following transplantation, patient and graft survival 24 and 36 months after transplantation, renal function at 6, 12, 24, and 36 months, the effect on chronic rejection at 12 and 36 months, and quality of life and pharmacoeconomic outcomes through 36 months after transplantation.

This was non-investigational new drug (non-IND), phase 3, randomized, open-label, 2-part study conducted in Australia, Canada, and Europe. A total of 525 patients were enrolled in study 310. During the first 3 months of the study (when all patients received Rapamune, CsA, and corticosteroids), a total of 95 patients were either withdrawn from study medication or were not eligible for randomization (as described below); these patients are referred to as the nonrandomized group. Three (3) months following transplantation, the remaining 430 patients were randomly assigned to group A (subsequently referred to as the RAPA + CsA group, n = 215) or group B (subsequently referred to as the RAPA group, n = 215). Patients were excluded from randomization into groups RAPA + CsA or RAPA if they fulfilled any of the following criteria: Banff grade III acute rejection episode or vascular rejection in the 4 weeks before random assignment, dialysis dependency, serum creatinine > 400 μmol/L, or inadequate renal function (in the opinion of the investigator) to support CsA elimination. However, only a minority of enrolled patients were ineligible for randomization by these criteria.

Patients were stratified at the time of random assignment on the basis of donor source (living donor versus cadaver). Patients in the RAPA + CsA group received Rapamune (nominally 2 mg/day, whole blood trough sirolimus concentrations adjusted to a minimum of 5 ng/mL, determined by sirolimus immunoassay), along with CsA. Patients in the RAPA group had their daily Rapamune dose adjusted to maintain sirolimus trough concentrations of 20 to 30 ng/mL until 12 months and then 15 to 25 ng/mL thereafter; the CsA dose was gradually eliminated over the course of 4 to 6 weeks beginning at the 3-month randomization point. Patients in both groups, RAPA + CsA and RAPA, continued to receive corticosteroids.

5.2 Supportive RMR Study (Protocol 0468E1-212-GL)

Study 212 was an open-label, randomized, phase 2 study that was conducted under the US IND in Europe and the United States. A total of 246 primary renal transplant recipients were enrolled in the study. Patients with adequate renal function (as determined by the investigator) were randomly assigned to either group A or group B within 48 hours after transplantation. The patients in group A, subsequently referred to as the RAPA + CsA group, received fixed doses of Rapamune (2 mg/day) administered with standard doses of CsA and corticosteroids. The patients in group B, subsequently referred to as the RAPA group, received concentration-controlled sirolimus (dose adjusted to whole blood trough concentrations of 10 to 20 ng/mL) administered concomitantly with corticosteroids and low-dose, short-term CsA. Patients with prolonged acute tubular necrosis (ATN)/delayed graft function (DGF) were eligible for randomization if their ATN/DGF had resolved sufficiently by day 7 to allow them to receive CsA. Group C (subsequently referred to as the nonrandomized group) included those patients who were not randomly assigned to the RAPA + CsA or RAPA groups because their ATN/DGF had not resolved by day 7 after transplantation; however, these patients continued to receive CsA per local practice and were permitted to receive up to 5 mg Rapamune daily as a component of their immunosuppressive therapy.

Patients randomly assigned to the RAPA group began elimination of CsA, starting 2 months after transplantation, once sirolimus trough concentrations of 10 to 20 ng/mL were established. CsA doses were then tapered by 25% (of the original dose) per week until CsA was eliminated from the immunosuppressive regimen by the end of month 3. A total of 97 patients were randomly assigned to the RAPA + CsA group and 100 to the RAPA group; 49 patients entered the nonrandomized group. Daily treatment for all 3 groups continued for up to 12 months.

The primary objective of study 212 was to assess graft function at month 6 in patients in whom concentration-controlled sirolimus was used to allow for the elimination of CsA 2 to 3 months following transplantation. The analyses for the primary endpoint were performed on the valid-for-efficacy (VFE) population, which included patients who continued to receive study medication (Rapamune with or without standard dose CsA) and who did not have an acute rejection episode by 6 months. Patients were evaluated for the primary endpoint at month 6 after transplantation but continued to receive daily treatment for up to 12 months. Calculated and measured GFR at 2, 6, and 12 months were additional supportive measurements. The population for secondary analyses included all patients in the RAPA + CsA and RAPA groups who were receiving study drug at the corresponding time point. Secondary endpoints included the

incidence of biopsy-confirmed acute rejection 2, 6, and 12 months after transplantation, patient and graft survival 2, 6, and 12 months after transplantation, and the comparison of serum creatinine in the RAPA + CsA and RAPA groups 2 and 12 months after first administration of study drug.

5.3 Comparison of Studies 310 and 212

The designs of studies 310 and 212, though similar, were distinct, especially with regard to the time patients were randomly assigned to treatment in relation to the time of transplant. Therefore, it was not possible to integrate the data from the 2 studies. Study 310 is the pivotal study conducted worldwide in a total of 525 renal allograft patients. The supportive study, study 212, was also conducted worldwide in a total of 246 patients. Table 5.3A summarizes the design of studies 310 and 212.

TABLE 5.3A. COMPARISON OF STUDY DESIGN FOR STUDIES 310 AND 212

Important Aspects	Study 310	Study 212
Total patients enrolled	525	246
Time of randomization	Month 3 ± 2 weeks	Up to day 7
Total patients randomized	430	197
RAPA + CsA group (Rapamune 2 mg with CsA) (randomized/received study drug)	215/215	97/97
RAPA group (concentration-controlled sirolimus with CsA elimination) (randomized/received study drug)	215/215	100/99
Time of CsA elimination	Month 3	After month 2
Nonrandomized group - description	Patients who discontinued therapy before randomization (month 3)	Patients who were not eligible for randomization
Nonrandomized group (n)	95	49
Primary endpoint	Graft survival 1 year (RAPA + CsA vs RAPA)	Renal function at month 6 Valid-for-efficacy population (RAPA + CsA vs RAPA)
Sirolimus formulation	Tablet	Oral solution

Additional points regarding the design of the 2 studies are provided below:

Study 310 was conducted in Europe, Canada, and Australia. Only 2% of the patients were black, but with this exception, the population studied was generally comparable to the general renal transplant population in the United States. As noted above, the 95 patients (18%) who discontinued before randomization or did not meet eligibility criteria for randomization are referred to as the nonrandomized group. For this group of patients, the following is noteworthy:

- This rate of discontinuation was very similar to that observed in other immunosuppressive trials of renal allograft recipients.

- The varied reasons for discontinuation parallel those observed in other renal transplantation trials (infection, efficacy failure, surgical complications, etc).

- The exclusion of these 95 patients did not affect the overall patient demographics, which were similar at baseline (ie, enrollment) and at the time of randomization.

In study 212, the nonrandomized group consisted of the 49 patients who were ineligible for randomization. Rapamune therapy was continued in these patients with combination immunotherapy individualized for each patient. Patients who discontinued treatment after randomization into groups RAPA + CsA or RAPA and who received a protocol-mandated medication regimen could be switched to an individualized therapy if the investigator elected to continue Rapamune therapy as part of the patient's immunosuppressive regimen. Patients switched in this manner were managed in the same way as those who were in the nonrandomized group. In this regard, it is important to note the following:

- All analyses on the intent-to-treat (ITT) population for the RAPA + CsA and RAPA groups included all patients randomly assigned to the respective groups. In the case of the nonrandomized group, the ITT population includes only the 49 patients who were never randomized.

- The "on-therapy" analyses included all patients who were randomly assigned to the RAPA + CsA group or the RAPA group and were receiving Rapamune therapy at the corresponding time point. Any patient who was receiving Rapamune therapy and was switched from either the RAPA + CsA group or the RAPA group to individualized therapy was included in the patient's original (randomized RAPA + CsA or RAPA) group

analysis for the population receiving therapy (on-therapy population). For example, if a patient in the RAPA group discontinued the protocol-mandated regimen and was switched to individualized therapy at month 2 but continued to receive Rapamune until month 12, that patient's laboratory values were included in the on-therapy analyses for the RAPA group until month 12.

- The on-therapy analyses for the nonrandomized group included only those patients who were originally enrolled in this group and continued to receive Rapamune at the corresponding time point.

5.4 Demographic Characteristics of the Study Population

5.4.1 Renal Allograft Recipients

Table 5.4.1A shows demographic and baseline characteristics for all patients (ITT population) enrolled in study 310.

TABLE 5.4.1A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF RENAL ALLOGRAFT RECIPIENTS (ITT POPULATION): STUDY 310

Characteristic	RAPA + CsA (n = 215)	RAPA (n = 215)	RAPA + CsA vs RAPA p-Value	Nonrandomized (n = 95)	Total (n = 525)
Sex, n (%)			0.314[a]		
Female	72 (33)	82 (38)		35 (37)	189 (36)
Male	143 (67)	133 (62)		60 (63)	336 (64)
Ethnic origin, n (%)			0.689[a]		
White	201 (93)	205 (95)		90 (95)	496 (94)
Black	5 (2)	2 (<1)		1 (1)	8 (2)
Asian	4 (2)	3 (1)		3 (3)	10 (2)
Other	5 (2)	5 (2)		1 (1)	11 (2)
Age, years			0.317[b]		
Mean	45.8	44.6		48.8	45.9
Standard deviation	11.6	13.1		13.5	12.7
Minimum	16	16		21	16
Maximum	68	73		72	73
Median	47.0	45.0		52.0	47.0
Height, cm	(n = 208)[c]	(n = 207)[c]	0.135[b]	(n = 92)[c]	(n = 507)[c]
Mean	169.6	168.1		168.7	168.8
Standard deviation	10.3	9.1		9.4	9.7
Minimum	135	142		145	135
Maximum	196	198		191	198
Median	170.0	169.0		170.0	169.0
Weight, kg			0.001[b]	(n = 95)[c]	
Mean	70.5	66.5		73.6	69.4
Standard deviation	13.8	12.6		16.0	14.0
Minimum	42	38		44	38
Maximum	139	104		110	139
Median	70.0	65.2		73.2	68.6
Number of HLA mismatches		(n = 214)[c]	0.825[b]		(n = 524)[c]
Mean	2.9	3.0		2.9	2.9
Standard deviation	1.4	1.3		1.5	1.3
Minimum	0	0		0	0
Maximum	6	6		6	6
Median	3.0	3.0		3.0	3.0

TABLE 5.4.1A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF RENAL ALLOGRAFT RECIPIENTS (ITT POPULATION): STUDY 310

Characteristic	RAPA + CsA (n = 215)	RAPA (n = 215)	RAPA + CsA vs RAPA p-Value	Nonrandomized (n = 95)	Total (n = 525)
Transplant, n (%)		(n = 214)[c]	0.603[a]		
Primary	197 (92)	193 (90)		83 (87)	473 (90)
Secondary	18 (8)	21 (10)		12 (13)	51 (10)
CMV status, n (%)	(n = 214)[c]	(n = 212)[c]	0.866[a]		
Negative	59 (28)	60 (28)		36 (38)	155 (30)
Positive	155 (72)	152 (72)		59 (62)	366 (70)
Primary etiology, n (%)			0.749[a]		
Autoimmune disease	2 (<1)	5 (2)		3 (3)	10 (2)
Diabetes mellitus	14 (7)	17 (8)		11 (12)	42 (8)
Failure of previous graft	2 (<1)	3 (1)		3 (3)	8 (2)
Glomerulonephritis	49 (23)	44 (20)		30 (32)	123 (23)
Hypertension	15 (7)	11 (5)		6 (6)	32 (6)
IgA nephropathy (Berger's)	25 (12)	29 (13)		9 (9)	63 (12)
Interstitial nephritis/pyelonephritis	16 (7)	19 (9)		7 (7)	42 (8)
Obstructive uropathy/reflux	8 (4)	8 (4)		7 (7)	23 (4)
Other/unknown	53 (25)	59 (27)		7 (7)	119 (23)
Polycystic disease-kidney	31 (14)	20 (9)		12 (13)	63 (12)
Delayed graft function,[d] n (%)	47 (21.9)	41 (19.1)	0.473[a]	46 (48.4)	134 (25.5)
Acute graft rejection,[e] n (%)	20 (9.3)	22 (10.2)	0.871[f]	27 (28.4)	69 (13.1)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CMV = cytomegalovirus, HLA = human leukocyte antigen, IgA = immunoglobulin A.
a: Pearson chi-square test.
b: Analysis of variance (ANOVA) with treatment as factor.
c: Where the values for n differ from the total number of patients in the groups, they are provided (for height, number of HLA mismatches, transplant, and CMV status for each group).
d: Delayed graft function: patient required dialysis for ≤ 8 days after transplantation.
e: Prerandomization rejection for all groups.
f: Fisher's exact test.

In study 310, 64% of the renal allograft recipient patients were male, 94% of the patients were white, and only 2% were black. The patient demographics and baseline characteristics were similar for both the RAPA + CsA and RAPA treatment groups. The only significant difference in the demographic and baseline characteristics of study 310 was that patients enrolled in the RAPA + CsA group had higher body weights than those in the RAPA group; this may have been related to the higher percentage of men in the RAPA + CsA group.

Table 5.4.1B shows the demographic and baseline characteristics for the ITT population in study 212.

TABLE 5.4.1B. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF RENAL ALLOGRAFT RECIPIENTS (ITT POPULATION): STUDY 212

Characteristic	RAPA + CsA (n = 97)	RAPA (n = 100)	p-Value[a]	Nonrandomized (n = 49)	Total (n = 246)
Sex, n (%)			0.853[b]		
Female	42 (43)	42 (42)		19 (39)	103 (42)
Male	55 (57)	58 (58)		30 (61)	143 (58)
Ethnic origin, n (%)			0.245[b]		
White	71 (73)	80 (80)		31 (63)	182 (74)
Black	18 (19)	15 (15)		14 (29)	47 (19)
Oriental (Asian)	4 (4)	2 (2)		1 (2)	7 (3)
Hispanic	1 (1)	3 (3)		3 (6)	7 (3)
Other	3 (3)	0		0	3 (1)
Age, years			0.839[c]		
Mean	44.9	45.2		47.8	45.6
Standard deviation	12.9	11.7		12.8	12.4
Minimum	19	20		19	19
Maximum	69	71		75	75
Median	46.0	47.0		46.0	46.5
Height, cm	(n = 96)[d]	(n = 96)[d]	0.159[c]	(n = 48)[d]	(n = 240)[d]
Mean	168.3	170.4		168.9	169.3
Standard deviation	10.8	9.5		10.3	10.2
Minimum	145	148		146	145
Maximum	191	193		191	193
Median	166.0	170.0		169.5	168.5
Weight, kg	(n = 95)[d]		0.857[c]		(n = 244)[d]
Mean	73.4	73.0		74.2	73.4
Standard deviation	16.8	17.1		18.9	17.3
Minimum	43	45		48	43
Maximum	128	123		113	128
Median	72.3	69.8		72.5	70.9
Recipient CMV status, n (%)		(n = 99)[d]	0.650[b]		(n = 245)[d]
Positive	61 (63)	68 (69)		32 (65)	161 (66)
Negative	19 (20)	15 (15)		10 (20)	44 (18)
Not done	17 (18)	16 (16)		7 (14)	40 (16)
Number of HLA mismatches, n (%)			0.329[b]		
0 to 3	60 (62)	55 (55)		24 (49)	139 (57)
4 to 6	37 (38)	45 (45)		25 (51)	107 (43)

TABLE 5.4.1B. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF RENAL ALLOGRAFT RECIPIENTS (ITT POPULATION): STUDY 212

Characteristic	RAPA + CsA (n = 97)	RAPA (n = 100)	p-Value[a]	Nonrandomized (n = 49)	Total (n = 246)
Primary etiology, n (%)			0.684[b]		
Autoimmune disease	2 (2)	2 (2)		2 (4)	6 (2)
Diabetes mellitus	9 (9)	8 (8)		13 (27)	30 (12)
Glomerulonephritis	19 (20)	30 (30)		13 (27)	62 (25)
Hypertension	19 (20)	16 (16)		11 (22)	46 (19)
IgA nephropathy (Berger's)	9 (9)	8 (8)		1 (2)	18 (7)
Interstitial nephritis/ pyelonephritis	5 (5)	3 (3)		2 (4)	10 (4)
Obstructive uropathy/reflux	6 (6)	9 (9)		3 (6)[e]	18 (7)
Other/unknown	14 (14)	8 (8)		0	22 (9)
Polycystic disease-kidney	14 (14)	16 (16)		4 (8)	34 (14)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CMV = cytomegalovirus, HLA = human leukocyte antigen, IgA = immunoglobulin A.
a: p-Value compares RAPA + CsA with RAPA.
b: Pearson chi-square test.
c: Analysis of variance (ANOVA) with treatment as factor.
d: Where the values for n differ from the total number of patients in the groups, they are provided (for height, weight, and CMV status for each group).
e: One (1) patient in the nonrandomized group had a primary diagnosis of hydronephrosis, categorized in this table as obstructive uropathy.

The majority of patients (ITT population) in study 212 were male (58%) and white (74%); 19% of enrolled patients were black. The patient demographics and baseline characteristics were similar for the RAPA + CsA and RAPA treatment groups.

5.4.2 Renal Allograft Donors

Tables 5.4.2A and 5.4.2B show the demographic and baseline characteristics of the renal allograft donors for studies 310 and 212, respectively. The donors for patients in both studies were predominantly white (98% in study 310 and 88% in study 212). As per the protocol, all patients in study 212 received allografts from cadaveric donors. In study 310, 89% of the kidneys were obtained from cadavers.

In both studies 310 and 212, the randomized groups (RAPA + CsA and RAPA) were well matched with regard to the demography of the renal allograft donors. Compared with the randomized groups, the donors for the nonrandomized patients 1) were slightly older and more commonly cadaveric in study 310 and 2) were slightly older in study 212. A larger percentage of the donated organs in the nonrandomized group of study 212 had ischemia times ≥ 24 hours.

TABLE 5.4.2A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF RENAL ALLOGRAFT DONORS AND SOURCE OF DONOR ORGAN: STUDY 310

Characteristic	RAPA + CsA (n = 215)	RAPA (n = 215)	RAPA + CsA vs RAPA p-Value	Nonrandomized (n = 95)	Total (n = 525)
Donor ethnic origin, n (%)[a]	(n = 169)[b]	(n = 174)[b]	0.349[c]	(n = 76)[b]	(n = 419)[b]
Black	0	1 (<1)		0	1 (<1)
Oriental (Asian)	2 (1)	1 (<1)		2 (3)	5 (1)
Other	0	2 (1)		1 (1)	3 (<1)
White	167 (99)	170 (98)		73 (96)	410 (98)
Ischemia time, hours	(n = 213)[b]	(n = 211)[b]	0.090[d]	(n = 94)[b]	(n = 518)[b]
Mean	17.8	16.4		17.8	17.2
Standard deviation	9.3	8.8		7.9	8.9
Minimum	0	0		0	0
Maximum	47	43		46	47
Median	18.3	17.0		18.0	17.5
Donor age, years			0.116[d]	(n = 94)[b]	(n = 524)[b]
Mean	44.0	41.7		48.0	43.8
Standard deviation	15.0	15.9		16.8	15.8
Minimum	2	2		5	2
Maximum	77	72		75	77
Median	46.0	45.0		51.0	46.0
Donor CMV status, n (%)	(n = 211)[b]	(n = 210)[b]	0.340[c]	(n = 91)[b]	(n = 512)[b]
Negative	70 (33)	79 (38)		35 (38)	184 (36)
Positive	141 (67)	131 (62)		56 (62)	328 (64)
Source of donor organ, n (%)			0.985[c]		
Cadaver	189 (88)	190 (88)		89 (94)	468 (89)
Living related donor	19 (9)	18 (8)		4 (4)	41 (8)
Living unrelated donor	7 (3)	7 (3)		2 (2)	16 (3)

RAPA = Rapamune, CsA = cyclosporine, CMV = cytomegalovirus.

a: Complete demographic information was not available for all donors.

b: Where the values for n differ from the total number of patients in the groups, they are provided for each group.

c: Pearson chi-square test.

d: Analysis of variance with treatment as factor.

TABLE 5.4.2B. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF RENAL ALLOGRAFT DONORS (12-MONTH DATA): STUDY 212

Characteristic	RAPA + CsA (n = 97)	RAPA (n = 100)	p-Values[a]	Nonrandomized (n = 49)	Total (n = 246)
Donor ethnic origin, n (%)	(n = 92)[b]	(n = 95)[b]	0.087	(n = 47)[b]	(n = 234)[b]
Black	9 (10)	4 (4)		4 (9)	17 (7)
Hispanic	1 (1)	6 (6)		2 (4)	9 (4)
Asian	1 (1)	0		0	1 (< 1)
Other	0	0		1 (2)	1 (< 1)
White	81 (88)	85 (89)		40 (85)	206 (88)
Ischemia time, n (%)			0.448		
Less than 24 hours	86 (89)	85 (85)		33 (67)	204 (83)
24 hours or more	11 (11)	15 (15)		16 (33)	42 (17)
Donor age, n (%)			0.820		
Less than 50 years	76 (78)	77 (77)		35 (71)	188 (76)
50 years or greater	21 (22)	23 (23)		14 (29)	58 (24)
Donor CMV status, n (%)	(n = 97)[b]	(n = 99)[b]	0.074	(n = 48)[b]	(n = 244)[b]
Positive	70 (72)	75 (76)		29 (59)	174 (71)
Negative	27 (28)	20 (20)		18 (37)	65 (27)
Not done	0	4 (4)		1 (2)	5 (2)

RAPA = Rapamune, CsA = cyclosporine, CMV = cytomegalovirus.
a: Pearson's chi-square test compares RAPA + CsA with RAPA.
b: Where values for n differ from the total number of patients in the groups, they are provided for each group.

6 EFFICACY

6.1 Overview of Results of Pivotal and Supportive Studies

Data are presented from studies in renal allograft recipients demonstrating the efficacy of a regimen using Rapamune (sirolimus, rapamycin) and corticosteroids with a short course of microemulsion CsA (Neoral) for the first several months following transplantation. Rapamune has previously been shown to effectively prevent acute organ rejection in patients receiving renal transplants when used in combination with CsA and corticosteroids. The current summary provides evidence for an effective therapeutic regimen, utilizing Rapamune and corticosteroids with short-term CsA, that results in an improved safety profile without compromising immunosuppressive efficacy. These data are based on a pivotal study, study 310 (an adequate and well-controlled phase 3 RMR study), conducted with 525 patients. Additional supportive data were obtained from study 212 (supportive RMR study). Twelve (12)-month data are presented for studies 310 and 212. Additional safety data beyond 12 months are presented for study 310.

Results of the primary endpoint analyses of studies 310 and 212 demonstrate that the combination of Rapamune, CsA, and corticosteroids in the early postoperative period, followed by the progressive elimination of CsA in conjunction with concentration-controlled sirolimus, is a safe and effective alternative to long-term CsA-based immunosuppression. At 12 months, comparable rates of acute rejection, graft survival, and patient survival as well as a statistically significant improvement in renal function were observed in the CsA-withdrawal group when compared with the group in which CsA was continued.

6.2 Primary Efficacy Endpoint

The primary endpoint for study 310 was the rate of graft survival at 12 months after transplantation, the rates for patients receiving continuous therapy with CsA and Rapamune (RAPA + CsA group) were compared with the rates for patients receiving induction with CsA and Rapamune followed by CsA elimination and continuation of concentration-controlled sirolimus (RAPA group). Graft loss was defined as physical loss (nephrectomy), functional loss (necessitating maintenance dialysis for more than 8 weeks), retransplant, or death.

The primary endpoint for study 212 was the serum creatinine level as assessed by comparing the levels between patients in the RAPA + CsA and RAPA groups (for patients who were receiving therapy and were rejection free 6 months after transplantation). Calculated Nankivell GFR[27] and

measured GFR (performed at centers selected by Wyeth-Ayerst Research [W-AR]) were additional supportive measurements.

6.3 Secondary Endpoints

For study 310, secondary endpoints included the following:

1. Comparison of serum creatinine levels between patients in the RAPA + CsA and RAPA groups 6, 12, 24, and 36 months after transplantation. Calculated GFR and measured GFR (at selected centers) were additional supportive measurements at these time points.
2. Incidence of biopsy-confirmed acute rejection 6 and 12 months after transplantation.
3. Histologic grade of first acute rejection episode after random assignment.
4. Patient survival 12, 24, and 36 months after transplantation.
5. Graft survival 24 and 36 months after transplantation.
6. Incidence of presumed or documented infection (confirmed by culture, biopsy, or serologic findings) 12, 24, and 36 months after transplantation.
7. Incidence of histologically confirmed lymphoproliferative disease 12, 24, and 36 months after transplantation.
8. Incidence of treatment failure (defined as the first occurrence of acute rejection, graft loss, death, or premature withdrawal from the study for any reason) analyzed separately during the pre- and postrandomization periods of the study.

Additional secondary endpoints will be evaluated, but data are not yet available.
For this report, 12-month efficacy analyses are provided, and safety data beyond 12 months are presented.

For study 212, secondary efficacy endpoints included the following:

1. Comparison of serum creatinine levels between patients in the RAPA + CsA and RAPA groups who were receiving therapy 2 and 12 months after administration of the first dose of study medication. Calculated GFR and measured GFR were additional supportive measurements.
2. Incidence of biopsy-confirmed acute rejection 2, 6, and 12 months after transplantation.

3. Patient and graft survival 2, 6, and 12 months after transplantation.
4. Incidence of presumed or documented infection (confirmed by culture, biopsy, or serology) 12 months after transplantation.
5. Incidence of histologically confirmed lymphoproliferative disease 12 months after transplantation.
6. Incidence of treatment failure (defined as the first occurrence of acute rejection, premature withdrawal of study medication for any reason, or conversion to individualized therapy within the first 6 months after transplantation).

6.4 Efficacy Results

6.4.1 Graft Survival

Table 6.4.1A summarizes the results for the rate of graft survival 12 months after transplantation for patients enrolled into study 310. Graft loss was defined as physical loss (nephrectomy), functional loss (necessitating maintenance dialysis for > 8 weeks), retransplant, death, or patients who were lost to follow-up. It should be noted that study 310 was designed primarily to assess the equivalence in the rates of graft survival 12 months after transplantation.

TABLE 6.4.1A. SUMMARY OF GRAFT SURVIVAL 12 MONTHS AFTER TRANSPLANT (ITT POPULATION): STUDY 310

Status	RAPA + CsA (n = 215)	RAPA (n = 215)	(RAPA + CsA) – (RAPA)[a] % (95% CI)	Nonrandomized (n = 95)	Total (n = 525)
Overall rate of graft survival, n (%)	206 (95.8)	209 (97.2)	-1.4 (-4.9 to 2.1)	53 (55.8)	468 (89.1)
Reason for graft failure, n (%)					
Pure graft loss[b]	5 (2.3)	2 (< 1)		28 (29.5)	35 (6.7)
Death with a functioning graft	4 (1.9)	4 (1.9)		13 (13.7)	21 (4)
Lost to follow-up	0	0		1 (1.1)	1 (< 1)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Difference is rate of (RAPA + CsA) group – rate of RAPA group; difference < 0 favors RAPA group.
b: Pure graft loss is defined as physical or functional loss in a living patient.

In study 310, the majority of the graft losses and deaths reported occurred during the first 3 months following transplantation, before randomization had occurred. The overall rate of graft survival at 12 months was 95.8% and 97.2% in the RAPA + CsA and RAPA groups, respectively. Based on the criteria for equivalence defined by the protocol, these data show

equivalent graft survival in the RAPA + CsA and RAPA groups at 12 months. Overall 12-month graft survival (groups RAPA + CsA, RAPA, and the nonrandomized patients) was 89.1%.

Table 6.4.1B summarizes the results for the rate of graft survival for patients enrolled into study 310 as of the data cutoff date, 03 Jan 2001.

TABLE 6.4.1B. SUMMARY OF GRAFT SURVIVAL AFTER TRANSPLANT (CUMULATIVE DATA—ITT POPULATION): STUDY 310

Status	RAPA + CsA (n = 215)	RAPA (n = 215)	(RAPA + CsA) – (RAPA)[a] % (95% CI)	Nonrandomized (n = 95)	Total (n = 525)
Overall rate of graft survival, n (%)	195[b] (90.7)	204[c] (94.9)	-4.2 (-9.1 to 0.7)	52 (54.7)	451 (85.9)
Reason for graft failure, n (%)					
Pure graft loss[d]	9[b] (4.2)	3 (1.4)		29 (30.5)	41 (7.8)
Death with a functioning graft	10[b] (4.7)	8[c] (3.7)		13 (13.7)	31 (5.9)
Lost to follow-up	1[e] (<1)	0		1 (1.1)	2 (< 1)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Difference is rate of (RAPA + CsA) group – rate of RAPA group; difference < 0 favors RAPA group.
b: 2 patients not yet in database included in statistical analysis.
c: 4 patients not yet in database included in statistical analysis.
d: Pure graft loss is defined as physical or functional loss in a living patient.
e: Patient 31050-5012, not yet in database, included in statistical analysis.

The overall rate of graft survival was 90.7% and 94.9% in the RAPA + CsA and RAPA groups, respectively. Overall graft survival (groups RAPA + CsA, RAPA, and the nonrandomized patients) was 85.9%. There was no statistical difference in graft survival between the RAPA + CsA and RAPA groups.

Table 6.4.1C summarizes the results for the graft survival data at 12 months for the ITT population in study 212. Graft loss was defined as physical loss (nephrectomy), functional loss (necessitating maintenance dialysis for > 8 weeks), retransplant, death, or patients who were lost to follow-up.

TABLE 6.4.1C. SUMMARY OF GRAFT SURVIVAL 12 MONTHS AFTER TRANSPLANT (ITT POPULATION): STUDY 212

Time	RAPA + CsA (n = 97)	RAPA (n = 100)	Nonrandomized (n = 49)
Month 12 (≤ 379 days)			
Graft survival, n (%)	90 (92.8)	95 (95.0)[a]	38 (77.6)
Graft loss, n (%)	4 (4.1)	1 (1.0)	6 (12.2)
Patient death, n (%)	3 (3.1)	4 (4.0)	4 (8.2)
Lost to follow-up, n (%)	0	0	1 (2.0)
Fisher's exact p-value[b]	0.564		
Difference in rate,[c] 95% CI	-2.2 (-8.9 to 4.5)		

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Survival includes 1 patient (21208-0819) who had an early 1 year visit (day 308 after transplant) and was ground-ruled as no event.
b: Fisher's exact test compares RAPA + CsA with RAPA.
c: Difference is rate of (RAPA + CsA) group – rate of RAPA group; difference < 0 favors RAPA group.

Graft survival rates at 12 months in study 212 for the RAPA + CsA and RAPA groups were 92.8% and 95%, respectively. Not surprisingly, the graft survival rate in the nonrandomized patients was lower (77.6%, month 12) than that observed in the RAPA + CsA and RAPA groups. Because many of the nonrandomized patients had experienced ATN/DGF in the immediate postoperative period, they were considered to be at higher risk for graft loss. There was no statistical difference in graft survival between the RAPA + CsA and RAPA groups.

6.4.2 Patient Survival

Table 6.4.2A shows patient survival 12 months after transplantation for all patients enrolled in study 310 (ITT population).

TABLE 6.4.2A. PATIENT SURVIVAL AT 12 MONTHS (ITT POPULATION): STUDY 310

Status	RAPA + CsA (n = 215)	RAPA (n = 215)	Nonrandomized (n = 95)	Total (n = 525)
Patient survival, n (%)	209 (97.2)	211 (98.1)	78 (82.1)	498 (94.9)
Patient death, n (%)	6 (2.8)	4 (1.9)	17 (17.9)	27 (5.1)
Fisher's exact p-value[a]	0.751			
Difference in rate[b] (95% CI)	-0.9 (-3.8 to 1.9)			

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Fisher's exact p-value compares groups RAPA + CsA with RAPA.
b: Difference in rate for patient survival is rate of RAPA + CsA – rate of RAPA. A difference < 0 favors RAPA.

In study 310, overall patient survival, including the nonrandomized patients, was 94.9% at the month 12 time point. There were no statistically significant differences in patient survival between the RAPA + CsA and RAPA groups (97.2% and 98.1%, respectively) at this time point.

Table 6.4.2B shows patient survival after transplantation for all patients enrolled in study 310 (ITT population) up to the data cutoff date of 03 Jan 2001.

TABLE 6.4.2B. PATIENT SURVIVAL (CUMULATIVE DATA—ITT POPULATION): STUDY 310

Status	RAPA + CsA (n = 215)	RAPA (n = 215)	Nonrandomized (n = 95)	Total (n = 525)
Patient survival, n (%)	203 (94.4)[a]	207 (96.3)[a]	78 (82.1)	488 (93.0)
Patient death, n (%)	12 (5.6)[a]	8 (3.7)[a]	17 (17.9)	37 (7.0)
Fisher's exact p-value[b]	0.493			
Difference in rate[c] (95% CI)	–1.9 (-5.8 to 2.1)			

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Includes 2 patients in RAPA + CsA group and 4 patients in RAPA group not yet in database.
b: Fisher's exact p-value compares groups RAPA + CsA with RAPA.
c: Difference in rate for patient survival is rate of RAPA + CsA – rate of RAPA. A difference < 0 favors RAPA.

In study 310, overall patient survival, including the nonrandomized patients, was 93.0%. There were no statistically significant differences in patient survival between the RAPA + CsA and RAPA groups (94.4% and 96.3%, respectively).

Table 6.4.2C shows patient survival (for all patients; ITT population) in study 212 at 12 months.

TABLE 6.4.2C. PATIENT SURVIVAL AT 12 MONTHS (ITT POPULATION): STUDY 212

Time	RAPA + CsA (n = 97)	RAPA (n = 100)	Nonrandomized (n = 49)
Month 12 (≤ 379 days)			
Patient survival, n (%)	94 (96.9)	96 (96.0)[a]	44 (89.8)[b]
Patient death, n (%)	3 (3.1)	4 (4.0)	4 (8.2)
Lost to follow-up, n (%)	0	0	1 (2.0)
Fisher's exact p-value[c]	1.000		
Difference in rate[d] (95% CI)	0.9 (-4.3 to 6.1)		

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Survival includes 1 patient (21208-0819) who had an early 1 year visit (day 308 after transplant) and was ground-ruled as no event.
b: Includes 1 patient (21206-0625) lost to follow-up and scored as patient death.
c: Fisher's exact test compares RAPA + CsA with RAPA..
d: Difference is rate of RAPA + CsA – rate of RAPA; a difference < 0 favors RAPA..

Patient survival for study 212 was > 89% for all patient groups in the study at 12 months after transplantation. There were no statistically significant differences in patient survival between the RAPA + CsA and RAPA groups.

6.4.3 Biopsy-Confirmed Acute Rejection

6.4.3.1 First Biopsy-Confirmed Acute Rejection

Acute rejection was confirmed by biopsy (Banff grades I, II, or III) as interpreted by designated local pathologists blinded to the treatment groups. Table 6.4.3.1A shows the incidence of the first biopsy-confirmed acute rejection episode at 12 months in study 310.

TABLE 6.4.3.1A. NUMBER (%) OF PATIENTS EXPERIENCING FIRST BIOPSY-CONFIRMED ACUTE REJECTION 12 MONTHS AFTER TRANSPLANT (ITT POPULATION): STUDY 310

Period	RAPA + CsA	RAPA	p-Value[a]	Nonrandomized	Total
Prerandomization	20/215 (9.3)	22/215 (10.2)	0.871	27/95 (28.4)	69/525 (13.1)
Postrandomization	6/215 (2.8)	21/215 (9.8)	0.005	-	27/430 (6.3)
Follow-up[b]	3/37 (8.1)	0/58 (0.0)	0.056	7/94[c] (7.4)	10/189 (5.3)
Postrandomization + follow-up	9/215 (4.2)	21/215 (9.8)	0.036	7/94[c] (7.4)	37/524 (7.1)
Total on-therapy	26/215 (12.1)	43/215 (20.0)	0.035	27/95 (28.4)	96/525 (18.3)
Total	29/215 (13.5)[d]	43/215 (20.0)[d]	0.093	34/95 (35.8)	106/525 (20.2)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Fisher's exact test compares RAPA + CsA with RAPA.
b: Follow-up is defined as the period after discontinuation of Rapamune treatment.
c: One (1) patient (310-5605) failed to return and never entered the follow-up period.
d: Difference in rate (95% confidence interval) is the rate of RAPA + CsA – the rate of RAPA, and is equal to –6.5 (-13.5, 0.5). Differences greater than zero favor the RAPA group.

The overall incidence of acute rejection in the entire study population (ITT) in study 310 was 20.2% at 12 months following transplantation. At this time point, the overall rate of acute rejection was not statistically significantly different between groups RAPA + CsA (13.5%) and RAPA (20%).

Table 6.4.3.1B shows the incidence of the first biopsy-confirmed acute rejection episode at 12 months in study 310.

TABLE 6.4.3.1B. NUMBER (%) OF PATIENTS EXPERIENCING FIRST BIOPSY-CONFIRMED ACUTE REJECTION BEFORE MONTH 3, BETWEEN MONTHS 3 AND 12, AND 12 MONTHS AFTER TRANSPLANT (ITT POPULATION): STUDY 310

Period	RAPA + CsA (n = 215)	RAPA (n = 215)	p-Value[a]
Incidence before month 3	20 (9.3)	22 (10.2)	0.871
New incidence months 3 to 12	9 (4.2)	21 (9.8)	0.036
Total incidence at month 12	29 (13.5)	43 (20.0)	0.093

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Fisher's exact test compares RAPA + CsA with RAPA.

Although the incidence of acute rejection between months 3 and 12 was significantly higher in the patients who had CsA eliminated (the RAPA group), the overall incidence at 12 months was not significantly different between the 2 groups.

Table 6.4.3.1C shows the incidence of the first biopsy-confirmed acute rejection episode in study 310 up to the data cutoff date of 03 Jan 2001.

TABLE 6.4.3.1C. NUMBER (%) OF PATIENTS EXPERIENCING FIRST BIOPSY-CONFIRMED ACUTE REJECTION AFTER TRANSPLANT (CUMULATIVE DATA - ITT POPULATION): STUDY 310

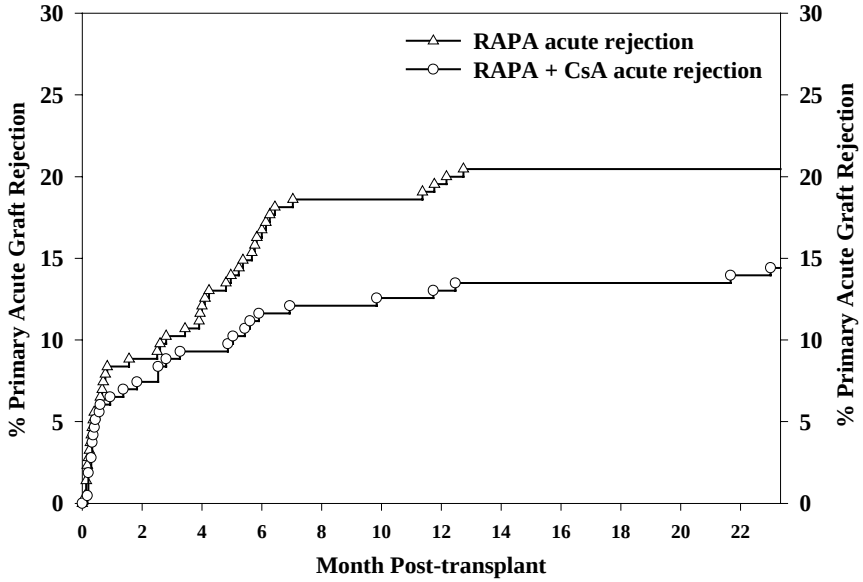
Period	RAPA + CsA	RAPA	p-Value[a]	Nonrandomized	Total
Prerandomization	20/215 (9.3)	22/215 (10.2)	0.871	27/95 (28.4)	69/525 (13.1)
Postrandomization	7[c]/215 (3.3)	22/215 (10.2)	0.006	-	29/430 (6.7)
Follow-up[b]	4/67 (6.0)	0/70 (0.0)	0.055	7/94[d] (7.4)	11/231 (4.8)
Postrandomization + follow-up	11[c]/215 (5.1)	22/215 (10.2)	0.069	7/94[d] (7.4)	40/524 (7.6)
Total on-therapy	27[c]/12.6)	44/215 (20.5)	0.037	27/95 (28.4)	98/525 (18.7)
Total	31[c]/215 (14.4)	44/215 (20.5)	0.127	34/95 (35.8)	109/525 (20.8)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Fisher's exact test compares RAPA + CsA with RAPA.
b: Follow-up is defined as the period after discontinuation of Rapamune treatment.
c: Patient 31033-3302, not yet in database, included in this statistical analysis.
d: One (1) patient (31056-5605) failed to return and never entered the follow-up period.

The overall incidence of acute rejection in the entire study population (ITT) in study 310 was 20.8%. The overall rate of acute rejection was not statistically significantly different between groups RAPA + CsA (14.4%) and RAPA (20.5%).

Figure 6.4.3.1A shows the time to first acute rejection for both the RAPA + CsA and the RAPA group for study 310.

FIGURE 6.4.3.1A. TIME TO FIRST ACUTE REJECTION: STUDY 310



Differences between groups in the time to first acute rejection were compared by using the log rank test and were found to be not significant (p = 0.101). Most of the acute rejection episodes in the RAPA group after randomization occurred during the first 3 months following randomization. Two (2) acute rejections in the RAPA + CsA group and 3 in the RAPA group were diagnosed by the 12-month protocol-mandated biopsy. None of the late rejection episodes in these patients were clinically symptomatic at the time of the 12-month biopsy; ie, they were subclinical rejection episodes. No acute rejection episodes were detected in the RAPA group and 2 episodes were detected in the RAPA + CsA group after 12 months.

Table 6.4.3.1D shows the incidence of first biopsy-confirmed acute rejection episode at various time points for the ITT patient population of study 212. Acute rejection was confirmed by biopsy (Banff grade I, II, or III) as interpreted by designated local pathologists blinded to treatment assignment.

TABLE 6.4.3.1D. NUMBER (%) OF PATIENTSWITH FIRST BIOPSY-CONFIRMED ACUTE REJECTION AFTER TRANSPLANT (ITT POPULATION): STUDY 212

Time	RAPA + CsA (n = 97)	RAPA (n = 100)	Nonrandomized (n = 49)
Month 2 (≤ 74 days)			
Acute rejection, n (%)	12 (12.4)	8 (8.0)	7 (14.3)
Fisher's exact p-value[a]	0.352		
Difference in rate[b], (90% CI)	-4.4 (-11.5 to 2.7)		
Difference in rate[b], (95% CI)	-4.4 (-12.9 to 4.1)		
Month 6 (≤ 194 days)			
Acute rejection, n (%)	15 (15.5)	18 (18.0)	9[c] (18.4)
Fisher's exact p-value[a]	0.705		
Difference in rate[b], (90% CI)	2.5 (-6.2 to 11.3)		
Difference in rate[b], (95% CI)	2.5 (-7.9 to 13.0)		
Month 12 (≤ 379 days)			
Acute rejection, n (%)	18 (18.6)	22[d] (22.0)	10[c] (20.4)
Fisher's exact p-value[a]	0.598		
Difference in rate[b], (90% CI)	3.4 (-6.0 to 12.9)		
Difference in rate[b], (95% CI)	3.4 (-7.8 to 14.7)		
Acute rejection between months 2 and 6			
Acute rejection, n (%)	3 (3.1)	10 (10.0)	2 [c] (4.1)
Fisher's exact p-value[a]	0.082		
Difference in rate[b], (90% CI)	6.9 (1.2 to 12.6)		
Difference in rate[b], (95% CI)	6.9 (0.1 to 13.8)		
Acute rejection between months 2 and 12			
Acute rejection, n (%)	6 (6.2)	14 (14.0)	3 [c] (6.1)
Fisher's exact p-value[a]	0.098		
Difference in rate[b], (90% CI)	NA		
Difference in rate[b], (95% CI)	NA		

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval, NA = not available.

a: Fisher's exact p-value compares RAPA + CsA with RAPA.

b: Difference is rate of RAPA – rate of RAPA + CsA, difference < 0 favors RAPA. 90% CI included per protocol specification.

c: Includes 1 patient (21206-0625) who was lost to follow-up and was scored as having acute rejection.

d: Patient 21208-0819 had an early 12-month visit (day 308 after transplant) and was ground-ruled as no event.

No statistically significant differences in the incidence of acute rejection episodes between the RAPA + CsA and RAPA groups were found at months 2, 6, or 12 following transplantation in study 212. Similarly, there were no statistically significant differences in the incidence of acute rejection episodes between the RAPA + CsA and RAPA groups during the intervals between months 2 and 6 or months 2 and 12. The overall rates of acute rejection in all groups were ≤ 22%.

6.4.3.2 Severity of Biopsy-Confirmed Acute Rejection

Table 6.4.3.2A shows the grade of biopsy-confirmed acute rejection at 12 months for study 310. The histologic grades of acute rejections were classified as mild (grade I), moderate (grade IIA or IIB), or severe (grade III).

TABLE 6.4.3.2A. NUMBER (%) OF PATIENTS WITH FIRST BIOPSY-CONFIRMED-ACUTE REJECTION BY GRADE AT 12 MONTHS (ITT POPULATION): STUDY 310

Period	Grade of Rejection	RAPA + CsA	RAPA	p-Value[a] RAPA + CsA vs RAPA	Nonrandomized
Prerandomization	Mild	12/20[b] (60.0)	10/22 (45.5)		9/27 (33.3)
	Moderate (IIA)	3/20 (15.0)	4/22 (18.2)		7/27 (25.9)
	Moderate (IIB)	4/20 (20.0)	6/22 (27.3)	0.336	5/27 (18.5)
	Severe	1/20 (5.0)	2/22 (9.1)		6/27 (22.2)
Postrandomization	Mild	5/6 (83.3)	14/21 (66.7)		-
	Moderate (IIA)	1/6 (16.7)	6/21 (28.6)	0.421	-
	Moderate (IIB)	-	1/21 (4.8)		-
	Severe	-	-		
Follow-up	Mild	2/3 (66.7)	-		3/7 (42.9)
	Moderate (IIA)	-	-		
	Moderate (IIB)	1/3 (33.3)	-	-	2/7 (28.6)
	Severe	-	-		2/7 (28.6)
Total[c]	Mild	19/29 (65.5)	24/43 (55.8)		12/34 (35.3)
	Moderate (IIA)	4/29 (13.8)	10/43 (23.3)		7/34 (20.6)
	Moderate (IIB)	5/29 (17.2)	7/43 (16.3)	0.514	7/34 (20.6)
	Severe	1/29 (3.4)	2/43 (4.7)		8/34 (23.5)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Cochran-Mantel-Haenszel (CMH) test (row mean scores differ). Row mean score tests the null hypothesis that the distribution of severities for the 2 groups is the same. The null-hypothesis is rejected for $p < 0.05$.
b: Denominator = number of first biopsy-confirmed acute rejections.
c: Includes 1 first biopsy-confirmed acute rejection (patient 310-7607) not entered in the database that occurred during the prerandomization period.

Table 6.4.3.2B shows the grade of biopsy-confirmed acute rejection for study 310 up to the data cutoff of 03 Jan 2001.

TABLE 6.4.3.2B. NUMBER (%) OF PATIENTS WITH FIRST BIOPSY-CONFIRMED ACUTE REJECTION BY GRADE (CUMULATIVE DATA—ITT POPULATION): STUDY 310

Period	Grade of rejection	RAPA + CsA	RAPA	p-Value[a] RAPA + CsA vs RAPA	Nonrandomized
Prerandomization	Mild	12/20[b] (60.0)	10/22 (45.5)		9/27 (33.3)
	Moderate (IIA)	3/20 (15.0)	4/22 (18.2)		7/27 (25.9)
	Moderate (IIB)	4/20 (20.0)	6/22 (27.3)	0.336	5/27 (18.5)
	Severe	1/20 (5.0)	2/22 (9.1)		6/27 (22.2)
Postrandomization[c]	Mild	6/7 (85.7)	15/22 (68.2)		-
	Moderate (IIA)	1/7 (14.3)	6/22 (27.3)	0.360	-
	Moderate (IIB)	-	1/22 (4.5)		-
	Severe	-	-		
Follow-up	Mild	2/3 (66.7)	-		3/7 (42.9)
	Moderate (IIA)	-	-		-
	Moderate (IIB)	1/3 (33.3)	-	-	2/7 (28.6)
	Severe	-	-		2/7 (28.6)
Total	Mild	20/30 (66.7)	25/44 (56.8)		12/34 (35.3)
	Moderate (IIA)	4/30 (13.3)	10/44 (22.7)		7/34 (20.6)
	Moderate (IIB)	5/30 (16.7)	7/44 (15.9)	0.492	7/34 (20.6)
	Severe	1/30 (3.3)	2/44 (4.5)		8/34 (23.5)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Cochran-Mantel-Haenszel (CMH) test (row mean scores differ). Row mean score tests the null hypothesis that the distribution of severities for the 2 groups is the same. The null hypothesis is rejected for $p < 0.05$.
b: Denominator = number of first biopsy-confirmed acute rejections.
c: Does not include 1 first biopsy-confirmed acute rejection (RAPA + CsA patient 31033-3302) not entered in the database that occurred during the postrandomization period.

In study 310, the majority of acute rejection episodes were mild, and there were no significant differences in the severity between the RAPA + CsA and RAPA groups either before or after randomization. Severe (grade III) acute rejection episodes did not occur after randomization in either group. A total of 9 patients experienced severe acute rejections while receiving therapy during the prerandomization period: 3 patients subsequently were randomly assigned and remained in the study. Of the remaining 6 nonrandomized patients, 2 patients continued to receive Rapamune in a compassionate-use study, 1 patient received alternative immunosuppressive therapy, 2 patients had graft loss, and 1 patient later died.

Table 6.4.3.2C shows the histologic grade of biopsy-confirmed acute rejection at various time points for the ITT population of study 212. The grades of acute rejections were classified as mild (grade I), moderate (grade IIA or IIB), or severe (grade III).

TABLE 6.4.3.2C. NUMBER (%) OF PATIENTS EXPERIENCING FIRST BIOPSY-CONFIRMED-ACUTE REJECTION BY GRADE (ITT POPULATION): STUDY 212

Time Severity	RAPA + CsA (n = 97)	RAPA (n = 100)	Nonrandomized (n = 49)
Month 2 (≤ 74 days), n	12	8	7
Mild	7 (58.3)[a]	7 (87.5)	4 (57.1)
Moderate	5 (41.7)	1 (12.5)	2 (28.6)
Severe	0	0	1 (14.3)
p-Value[b]	0.174		
Month 6 (≤ 194 days), n	15	18	8[c]
Mild	7 (46.7)	9 (50.0)	5 (62.5)
Moderate	7 (46.7)	9 (50.0)	2 (25.0)
Severe	1 (6.7)	0	1 (12.5)
p-Value[b]	0.612		
Month 12 (≤ 379 days), n	18	22	9[c]
Mild	9 (50.0)	9 (40.9)	6 (66.7)
Moderate	8 (44.4)	13 (59.1)	2 (22.2)
Severe	1 (5.6)	0	1 (11.1)
p-Value[b]	0.840		

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: The denominator used in the calculation of the percentage is the number of patients with acute rejection at that time point.
b: Row mean score test comparison of severity in patients with rejection (RAPA + CsA vs RAPA).
c: Does not include 1 patient (21206-0625) who was lost to follow-up and was scored as having acute rejection.

In this study, the majority of acute rejection episodes were mild or moderate. There were no statistically significant differences in histologic severity of acute rejection between the RAPA + CsA and RAPA groups at any time point.

6.4.3.3 Antibody Treatment of Biopsy-Confirmed Acute Rejection and Antibody Prophylaxis in the Early Postoperative Period

Table 6.4.3.3A shows the number and percentage of patients in study 310 receiving antithymocyte globulin (ATG) or muromonab-CD3 (Orthoclone; OKT3) for the treatment of acute rejection.

TABLE 6.4.3.3A. NUMBER (%) OF PATIENTS RECEIVING ANTI-T-CELL ANTIBODY FOR THE TREATMENT OF FIRST BIOPSY-CONFIRMED ACUTE REJECTION (ITT POPULATION): STUDY 310

Period	RAPA + CsA (n = 215)	RAPA (n = 215)	p-Value[a]	Nonrandomized (n = 95)	Total (n = 525)
Prerandomization	6 (2.8)	4 (1.9)	0.751	10 (10.5)	20 (3.8)
Postrandomization	0	2 (0.9)	0.499	-	2 (0.4)
Follow-up[b]	0	0	-	5 (5.3)	5 (1.0)
Total	6 (2.8)	6 (2.8)	1.000	15 (15.8)	27 (5.1)

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Fisher's exact test compares RAPA + CsA with RAPA.
b: Follow-up is defined as the period after discontinuation of Rapamune treatment.

In study 310, the percentage of patients who were receiving antibody therapies for the treatment of acute rejection during the prerandomization period (and who subsequently were randomly assigned to the RAPA + CsA or RAPA group) was 2.8% for the RAPA + CsA group and 1.9% for the RAPA group. By the 03 Jan 2001 data cutoff point, the use of ATG or OKT3 for the treatment of acute rejection was 5.1% in the total population and was the same in both the RAPA + CsA and RAPA groups (2.8%).

The percentage of patients in whom anti-T-cell antibody was administered for the treatment of acute rejection (includes first and subsequent rejections treated with antibody) during the first 12 months of study 212 is shown in Table 6.4.3.3B. There was no statistically significant difference between the RAPA + CsA and RAPA groups in the use of antibody.

TABLE 6.4.3.3B. NUMBER (%) OF PATIENTS TREATED WITH ANTI-T-CELL ANTIBODY FOR BIOPSY-CONFIRMED ACUTE GRAFT REJECTION AT 12 MONTHS (ITT POPULATION): STUDY 212

Antibody Treatment	RAPA + CsA (n = 97)	RAPA (n = 100)	Nonrandomized (n = 49)
n (%)	6 (6.2)	9 (9.0)	3 (6.1)
p-Value[a]	0.593		

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Fisher's exact test compares RAPA + CsA with RAPA.

Table 6.4.3.3C shows the number of patients in the ITT population of study 212 receiving antibodies for the prophylaxis of acute rejection episodes.

TABLE 6.4.3.3C. NUMBER (%) OF PATIENTS RECEIVING ANTI-T-CELL PROPHYLAXIS (ITT POPULATION): STUDY 212

Antibody Prophylaxis[a]	RAPA + CsA (n = 97)	RAPA (n = 100)	Nonrandomized (n = 49)
n (%)	15 (15.5)	7 (7.0)	22 (44.9)
p-Value[b]	0.072		

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: For antibody use to be considered prophylaxis, treatment had to occur after transplant and before randomization.
b: Fisher's exact test compares RAPA + CsA with RAPA.

In study 212, 15.5% and 7.0% of the patients in the RAPA + CsA and RAPA groups, respectively, received anti-T-cell antibody therapy for prophylaxis of acute rejection. Antibody use was considered to be prophylactic only if treatment was initiated before randomization. For the majority of patients, this occurred within the first 48 hours after transplantation, although prophylactic therapy could have been started before day 7 if ATN/DGF did not resolve during this period.

Table 6.4.3.3D shows the number of patients in whom either anti-T-cell antibody or anti-IL-2 receptor antibody was used for prophylaxis of acute rejection. For overall prophylactic antibody use, a statistically significantly greater number of patients in the RAPA + CsA group than in the RAPA group received antibody prophylaxis.

TABLE 6.4.3.3D. NUMBER (%) OF PATIENTS RECEIVING EITHER ANTI-T-CELL OR ANTI-IL-2R PROPHYLAXIS (ITT POPULATION): STUDY 212

Antibody Prophylaxis[a]	RAPA + CsA (n = 97)	RAPA (n = 100)	Nonrandomized (n = 49)
n (%)	19 (19.6)	9 (9.0)	40 (81.6)
p-Value[b]	0.041		

IL-2R = interleukin-2 receptor, ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: For antibody use to be considered prophylaxis, treatment had to occur after transplant and before randomization.
b: Fisher's exact test compares RAPA + CsA with RAPA.

The impact of the higher rate of antibody prophylaxis in the RAPA + CsA group on the difference in the rejection rates at month 12 is uncertain. There was no significant difference in the rates of rejection between patients who received antibody prophylaxis and those who did not (within the RAPA + CsA and RAPA groups, shown in Table 6.4.3.3E).

TABLE 6.4.3.3E. RELATIONSHIP OF ANTIBODY PROPHYLAXIS TO ACUTE REJECTION INCIDENCE: STUDY 212

Treatment Group (n)	Acute Rejection n (%)	Rejection-Free n (%)	Fisher's Exact p-Value
Antibody prophylaxis administered			
RAPA + CsA (n = 19)	3 (15.8)	16 (84.2)	1.000
RAPA (n = 9)	1 (11.1)	8 (88.9)	
Total (n = 28)	4 (14.3)	24 (85.7)	
No antibody prophylaxis administered			
RAPA + CsA (n = 78)	15 (19.2)	63 (80.8)	0.577
RAPA (n = 91)	21 (23.1)	70 (76.9)	
Total (n = 169)	36 (21.3)	133 (78.7)	
Prophylactic antibody use (n)			
RAPA + CsA			
Yes (n = 19)	3 (15.8)	16 (84.2)	1.000
No (n = 78)	15 (19.2)	63 (80.8)	
RAPA			
Yes (n = 9)	1 (11.1)	8 (88.9)	0.679
No (n = 91)	21 (23.1)	70 (76.9)	

RAPA = Rapamune, CsA = cyclosporine.

6.4.4 Renal Function Tests

This section presents analyses of the following renal function parameters for the on-therapy population: serum creatinine (studies 310 and 212), calculated GFR (studies 310 and 212), and measured GFR (study 212). The following additional analyses are presented for study 212 patient populations: serum creatinine (VFE and ITT populations), calculated GFR (VFE and ITT populations), and measured GFR (VFE population).

In study 310:

- The observed values were used to calculate the mean values for all groups.
- The analysis at month 3 represents an analysis of covariance (ANCOVA; comparison between the RAPA + CsA and RAPA groups) for those patients who were randomly assigned before the month 3 visit; the last prerandomization value was used as baseline. Because month 3 was the time of randomization, no statistical comparisons were made between the RAPA + CsA and RAPA groups values at months 1 and 2.
- No statistical comparisons were made using the values from the nonrandomized group.

In study 212:

- Observed values are presented for all 3 groups for tests of renal function (serum creatinine, calculated GFR, and measured GFR). The 2-group t test was used to make the comparisons between the RAPA + CsA and RAPA groups.

- No statistical comparisons are made by using the nonrandomized group values.

6.4.4.1 Serum Creatinine

Table 6.4.4.1A shows the mean serum creatinine values from study 310. The mean values for all on-therapy patients at the corresponding time periods are shown. The mean values for all on-therapy patients in study 212 are shown in Table 6.4.4.1B.

- In both studies, patients in the CsA-elimination arm (the RAPA group) had lower mean creatinine values than the patients maintained with CsA (the RAPA + CsA group). The comparison reached statistical significance at months 6 to 24 in study 310 and month 12 in study 212. Compared with the RAPA + CsA group value, the RAPA group value was approximately 10% (month 12) to 23% (month 24) lower in study 310 and 21% lower in study 212 at month 12.

- The serum creatinine values improved in the RAPA group in both studies: from months 2 to 24 in study 310 and from months 2 to 12 in study 212.

In both studies, the serum creatinine values were higher in the nonrandomized groups. Many of these patients had prolonged ATN/DGF or other risk factors for renal dysfunction.

TABLE 6.4.4.1A. OBSERVED MEAN VALUES (± SEM) FOR CREATININE (µmol/L): STUDY 310

Time (Posttransplant)	RAPA + CsA (n = 215)	RAPA (n = 215)	ANCOVA[a] RAPA + CsA vs RAPA p-Value	Nonrandomized (n = 95)
Month 1	169.5 ± 6.5 [1.92 ± 0.07][b] (212)[c]	162.4 ± 5.3 [1.84 ± 0.06] (212)	-	333.0 ± 29.6 [3.77 ± 0.33] (63)
Month 2	152.8 ± 3.5 [1.73 ± 0.04] (212)	154.5 ± 4.9 [1.75 ± 0.06] (201)	-	266.2 ± 30.3 [3.01 ± 0.34] (37)
Month 3	158.2 ± 3.9 [1.79 ± 0.04] (186)	154.8 ± 4.2 [1.75 ± 0.05] (193)	0.367	276.4 ± 48.4 [3.13 ± 0.55] (15)
Month 6	161.5 ± 4.3 [1.82 ± 0.05] (186)	149.9 ± 4.7 [1.70 ± 0.05] (183)	0.001	-
Month 9	157.1 ± 4.0 [1.78 ± 0.05] (185)	143.3 ± 4.7 [1.62 ± 0.05] (165)	<0.001	-
Month 12	158.1 ± 4.2 [1.79 ± 0.05] (185)	141.6 ± 5.3 [1.60 ± 0.06] (163)	<0.001	-
Month 15	160.3 ± 5.1 [1.81 ± 0.06] (155)	138.6 ± 5.6 [1.57 ± 0.06] (146)	<0.001	
Month 18	160.8 ± 4.8 [1.82 ± 0.05] (121)	134.5 ± 6.0 [1.52 ± 0.07] (111)	<0.001	
Month 21	163.2 ± 6.3 [1.85 ± 0.07] (62)	130.8 ± 5.7 [1.48 ± 0.06] (55)	<0.001	
Month 24	165.1 ± 9.7 [1.87 ± 0.11] (25)	127.3 ± 7.9 [1.44 ± 0.09] (22)	<0.001	

RAPA = Rapamune, CsA = cyclosporine, ANCOVA = analysis of covariance,
SEM = standard error of the mean.

a: For month 3 and subsequent months, the baseline used for ANCOVA analyses was the prerandomization observation. Observed means are used here throughout to allow comparisons with months 1 and 2.

b: Observed mean values ± SEM in mg/dL.

c: Number of observations used to calculate the mean.

TABLE 6.4.4.1B. OBSERVED MEAN VALUES ± SEM FOR SERUM CREATININE CONCENTRATIONS (µmol/L) FOR ALL PATIENTS ON THERAPY (12-MONTH DATA): STUDY 212

Time (Posttransplant)	RAPA + CsA	RAPA	t Test RAPA + CsA vs RAPA p-Value	Nonrandomized
Month 1 (week 4)	163.7 ± 9.8	161.0 ± 8.6	0.833	415.0 ± 60.5
	[1.85 ± 0.10][a]	[1.82 ± 0.10]		[4.69 ± 0.68]
	(84)[b]	(81)		(21)
Month 2 (week 8)	151.8 ± 6.2	148.7 ± 10.1	0.795	259.7 ± 32.8
	[1.72 ± 0.07]	[1.68 ± 0.10]		[2.94 ± 0.37]
	(76)	(76)		(16)
Month 3 (week 12)	155.3 ± 7.6	141.9 ± 5.4	0.153	214.3 ± 22.7
	[1.76 ± 0.09]	[1.61 ± 0.06]		[2.42 ± 0.26]
	(72)	(71)		(16)
Month 6	156.6 ± 7.1	139.2 ± 5.5	0.054	198.7 ± 17.0
	[1.77 ± 0.08]	[1.57 ± 0.06]		[2.25 ± 0.19]
	(82)	(82)		(23)
Month 9	155.2 ± 7.0	135.1 ± 7.5	0.054	216.6 ± 19.1
	[1.76 ± 0.08]	[1.53 ± 0.08]		[2.45 ± 0.27]
	(72)	(72)		(20)
Month 12	171.0 ± 9.5	135.7 ± 5.9	0.002	219.2 ± 22.6
	[1.93 ± 0.10]	[1.54 ± 0.07]		[2.48 ± 0.26]
	(76)	(77)		(23)

RAPA = Rapamune, CsA = cyclosporine, SEM = standard error of the mean.
a: Observed mean values ± SEM in mg/dL.
b: Number of observations used to calculate the mean.

6.4.4.2 Calculated GFR

The calculated Nankivell GFR values corresponding to the above-mentioned creatinine values are shown in Tables 6.4.4.2A and 6.4.4.2B for studies 310 and 212, respectively.

- The calculated GFR values were significantly higher in the RAPA group at months 6 to 24 for study 310 and months 6 to 12 for study 212. The mean value in the RAPA group was 18% higher than the corresponding value in the RAPA + CsA group at month 24 in study 310 and at month 12 in study 212.

- From months 3 to 18 (study 310) and months 1 to 12 (study 212), the GFR values improved in the RAPA group but remained unchanged (or decreased slightly) in the RAPA + CsA group.

TABLE 6.4.4.2A. OBSERVED MEAN VALUES (± SEM) FOR CALCULATED NANKIVELL GFR (mL/min): STUDY 310

Time (Posttransplant)	RAPA + CsA (n = 215)	RAPA (n = 215)	ANCOVA[a] RAPA + CsA vs RAPA p-Value	Nonrandomized (n = 95)
Month 1	54.7 ± 1.4 (205)[b]	54.6 ± 1.4 (205)	-	35.9 ± 2.9 (61)
Month 2	57.6 ± 1.2 (205)	56.1 ± 1.2 (193)	-	40.8 ± 3.5 (37)
Month 3	55.4 ± 1.2 (181)	55.9 ± 1.2 (185)	0.366	41.2 ± 5.4 (15)
Month 6	56.0 ± 1.4 (180)	58.6 ± 1.4 (176)	<0.001	
Month 9	56.7 ± 1.2 (178)	60.8 ± 1.5 (159)	<0.001	
Month 12	56.6 ± 1.3 (178)	62.7 ± 1.5 (158)	<0.001	
Month 15	56.4 ± 1.3 (150)	63.1 ± 1.7 (141)	<0.001	
Month 18	56.4 ± 1.5 (116)	64.9 ± 1.8 (107)	<0.001	
Month 21	55.6 ± 2.0 (60)	64.2 ± 2.1 (53)	<0.001	
Month 24	52.5 ± 3.2 (23)	63.9 ± 2.7 (21)	<0.001	

SEM = standard error of the mean, GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine, ANCOVA = analysis of covariance.

a: For month 3 and subsequent months, the baseline used for ANCOVA analyses was the prerandomization observation. Observed means are used here throughout to allow comparisons with months 1 and 2.

b: Number of observations used to calculate the mean.

TABLE 6.4.4.2B. MEAN VALUES ± SEM FOR NANKIVELL GFR (mL/min) FOR ON THERAPY PATIENTS (12-MONTH DATA): STUDY 212

Time (Posttransplant)	RAPA + CsA	RAPA	t Test RAPA + CsA vs RAPA p-Value	Nonrandomized
Month 1 (week 4)	56.79 ± 2.09 (82)[a]	57.88 ± 2.07 (78)	0.711	31.24 ± 3.86 (21)
Month 2 (week 8)	58.64 ± 1.88 (76)	61.94 ± 1.97 (73)	0.227	43.71 ± 4.37 (16)
Month 3 (week 12)	58.98 ± 1.83 (72)	62.25 ± 1.88 (71)	0.216	49.70 ± 4.74 (16)
Month 6	57.40 ± 1.71 (82)	65.17 ± 1.91 (82)	0.003	50.69 ± 2.81 (23)
Month 9	58.53 ± 1.91 (72)	68.17 ± 1.94 (72)	< 0.001	46.51 ± 2.99 (20)
Month 12	55.76 ± 2.05 (76)	68.25 ± 2.21 (77)	< 0.001	49.05 ± 3.30 (23)

GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine,
SEM = standard error of the mean.
a: Number of observations used to calculate the mean.

Table 6.4.4.2C shows the month 12 calculated GFR values for various subpopulations of the randomized groups RAPA + CsA and RAPA in study 310 and Table 6.4.4.2D shows 18-month data. The patients are categorized into various subpopulations generally considered to be at high risk for long-term graft dysfunction and/or graft loss. At the month 12 time point, it is noteworthy that patients in the CsA-elimination arm (RAPA group) had significantly better renal function than patients maintained on CsA (RAPA + CsA group) in the following populations: older patients, patients with DGF, recipients of kidneys from older donors, recipients of kidneys with ischemic time ≤ 24 hours, and recipients of kidneys from cadaveric donors. This statistical significance held true for the month 18 time point for all of the above categories other than patients with DGF. Additionally, the RAPA group recipients of kidneys from living donors had significantly better renal function than those in the RAPA + CsA group at the month 18 time point.

TABLE 6.4.4.2C. OBSERVED MEAN VALUES FOR CALCULATED NANKIVELL GFR (mL/min) FOR DIFFERENT SUBPOPULATIONS (12 MONTHS): STUDY 310

Characteristics of Subpopulation	RAPA + CsA	RAPA	ANCOVA[a] p-Value
Delayed graft function			
No	58.2 (144)[b]	64.9 (127)	<0.001
Yes	49.8 (34)	53.7 (31)	0.021
Donor age (years)			
≤ 50	60.9 (119)	66.8 (113)	<0.001
> 50	48.0 (59)	52.5 (45)	0.004
Donor ischemia time (hours)			
≤ 24	56.8 (146)	64.0 (134)	<0.001
> 24	55.0 (30)	55.9 (20)	0.069
Patient age (years)			
≤ 50	58.4 (111)	61.5 (107)	<0.001
> 50	53.6 (67)	65.4 (51)	<0.001
Living/cadaveric donor			
Living	62.2 (23)	61.9 (14)	0.053
Cadaveric	55.8 (155)	62.8 (144)	<0.001
Primary/secondary graft			
Primary	56.3 (163)	63.3 (142)	<0.001
Secondary	59.9 (15)	58.5 (15)	0.147

GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine,
ANCOVA = analysis of covariance.
a: The baseline used for ANCOVA analyses was the prerandomization observation.
b: Number of observations used to calculate the mean.

TABLE 6.4.4.2D. OBSERVED MEAN VALUES FOR CALCULATED NANKIVELL GFR (mL/min) FOR DIFFERENT SUBPOPULATIONS (18 MONTHS): STUDY 310

Characteristics of Subpopulation	RAPA + CsA	RAPA	ANCOVA[a] p-Value
Delayed graft function			
No	57.7 (95)[b]	66.3 (85)	<0.001
Yes	50.6 (21)	59.3 (22)	0.240
Donor age (years)			
≤ 50	59.5 (85)	69.3 (78)	<0.001
> 50	48.0 (31)	53.0 (29)	0.035
Donor ischemia time (hours)			
≤ 24	56.0 (95)	66.4 (90)	<0.001
> 24	57.1 (19)	57.5 (14)	0.158
Patient age (years)			
≤ 50	56.6 (78)	64.7 (73)	<0.001
> 50	56.0 (38)	65.3 (34)	0.001
Living/cadaveric donor			
Living	62.4 (14)	72.5 (6)	0.015
Cadaveric	55.6 (102)	64.4 (101)	<0.001
Primary/secondary graft			
Primary	55.9 (103)	64.9 (97)	<0.001
Secondary	60.5 (13)	65.6 (9)	0.490

GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine, ANCOVA = analysis of covariance.
a: The baseline used for ANCOVA analyses was the prerandomization observation.
b: Number of observations used to calculate the mean.

6.4.4.3 Measured GFR

In study 212, direct measurements of GFR were performed at selected sites by using a variety of approved radioisotope methods. Table 6.4.4.3A shows the means of the directly measured GFR values for all on-therapy patients in the RAPA + CsA and RAPA groups. A review of the data showed that many of the patients at 2 sites (sites 21211 and 21216) had values that were clearly erroneous (GFR values > 200 mL/min). In order to maintain consistency, all of the measured GFR values from these 2 sites have been excluded. The RAPA group had significantly higher measured GFR values at months 6 and 12; these results are consistent with the results of the calculated GFR.

TABLE 6.4.4.3A. MEAN VALUES ± SEM FOR MEASURED GFR (mL/min/1.73 m^2) FOR ALL PATIENTS ON THERAPY IN RAPA + CsA AND RAPA GROUPS (12-MONTH DATA): STUDY 212

Time (Posttransplant)	RAPA + CsA	RAPA	t Test p-Value
Month 6	52.20 ± 4.39 (42)[a]	64.58 ± 4.12 (50)	0.043
Month 12	49.13 ± 3.34 (44)	63.21 ± 3.46 (44)	0.004

GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine, SEM = standard error of the mean.
a: Number of observations.

In study 212, there were too few patients with measured GFR values in the nonrandomized group to present meaningful data.

In study 310, measured GFR values were available only for approximately 20 patients per randomized group. In this study, there was no protocol-mandated requirement to collect GFR values after the month 12 visit. The mean GFR value in the RAPA group was numerically higher than that in the RAPA + CsA group (data not shown).

6.4.4.4 VFE Population—Study 212

In study 212, the prospectively defined primary endpoint was the mean serum creatinine level in patients in the RAPA + CsA and RAPA groups who were rejection free and remained on therapy at month 6 (VFE population).

The mean values for serum creatinine, calculated GFR, and measured GFR for the VFE population are shown in Tables 6.4.4.4A, 6.4.4.4B, and 6.4.4.4C, respectively.

It is noteworthy that at months 6, 9, and 12, the mean serum creatinine value was significantly lower and the calculated and measured (months 6 and 12) GFR values were significantly higher in the CsA-elimination arm (RAPA group) than in the corresponding RAPA + CsA group values. At month 12, the mean creatinine values (± standard error of the mean [SEM]) were 161.3 ± 8.2 µmol/L (1.82 ± 0.09 mg/dL) and 122.1 ± 4.8 µmol/L (1.38 ± 0.05 mg/dL) in the RAPA + CsA and RAPA groups, respectively ($p < 0.001$). The corresponding calculated GFR values were 57.15 ± 2.23 mL/min and 73.49 ± 2.07 mL/min (the RAPA + CsA and RAPA groups, respectively, $p < 0.001$). The corresponding measured GFR values were

49.39 ± 3.63 mL/min and 67.11 ± 3.53 mL/min (the RAPA + CsA and RAPA groups, respectively, $p < 0.001$).

TABLE 6.4.4.4A. MEAN VALUES ± SEM FOR OBSERVED SERUM CREATININE CONCENTRATIONS (µmol/L) FOR SUBPOPULATIONS RAPA + CsA (VFE) AND RAPA (VFE) (12-MONTH DATA): STUDY 212

Time (Posttransplant)	RAPA + CsA (VFE)	RAPA (VFE)	t Test RAPA + CsA vs RAPA p-Value
Month 1 (week 4)	146.2 ± 6.7 [1.65 ± 0.08][a] (66)[b]	149.9 ± 9.5 [1.70 ± 0.10] (56)	0.747
Month 2 (week 8)	144.0 ± 6.5 [1.63 ± 0.07] (59)	134.2 ± 4.9 [1.52 ± 0.06] (55)	0.233
Month 3 (week 12)	150.4 ± 8.1 [1.70 ± 0.09] (62)	132.9 ± 4.7 [1.50 ± 0.05] (54)	0.065
Month 6	150.4 ± 7.3 [1.70 ± 0.08] (70)	126.6 ± 4.7 [1.43 ± 0.05] (64)	0.007
Month 9	151.2 ± 7.1 [1.71 ± 0.08] (63)	120.9 ± 4.2 [1.37 ± 0.05] (57)	< 0.001
Month 12	161.3 ± 8.2 [1.82 ± 0.09] (67)	122.1 ± 4.8 [1.38 ± 0.05] (60)	< 0.001

RAPA = Rapamune, CsA = cyclosporine, SEM = standard error of the mean, VFE = valid-for-efficacy.
a: Observed mean values ± SEM in mg/dL.
b: Number of observations used for the mean.

TABLE 6.4.4.4B. MEAN VALUES ± SEM FOR NANKIVELL GFR (mL/min) FOR PATIENTS IN SUBPOPULATIONS RAPA + CsA (VFE) AND RAPA (VFE) (12-MONTH DATA): STUDY 212

Time (Posttransplant)	RAPA + CsA (VFE)	RAPA (VFE)	t Test RAPA + CsA vs RAPA p-Value
Month 1 (week 4)	60.02 ± 2.15 (65)[a]	61.72 ± 2.23 (53)	0.586
Month 2 (week 8)	60.75 ± 1.94 (59)	64.06 ± 1.96 (53)	0.234
Month 3 (week 12)	59.89 ± 2.05 (62)	65.40 ± 1.89 (54)	0.053
Month 6	59.00 ± 1.86 (70)	69.37 ± 1.87 (64)	< 0.001
Month 9	59.53 ± 2.13 (63)	72.66 ± 1.70 (57)	< 0.001
Month 12	57.15 ± 2.23 (67)	73.49 ± 2.07 (60)	< 0.001

GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine,
SEM = standard error of the mean, VFE = valid-for-efficacy.
a: Number of observations used for the mean.

TABLE 6.4.4.4C. MEAN VALUES ± SEM FOR MEASURED GFR (mL/min/1.73 m^2) FOR SUBPOPULATIONS RAPA + CsA (VFE) AND RAPA (VFE) (12-MONTH DATA): STUDY 212

Time (Posttransplant)	RAPA + CsA (VFE)	RAPA (VFE)	t Test p-Value
Month 6	51.90 ± 4.90 (37)[a]	67.15 ± 4.29 (43)	0.021
Month 12	49.39 ± 3.63 (40)	67.11 ± 3.53 (36)	< 0.001

GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine,
SEM = standard error of the mean, VFE = valid-for-efficacy.
a: Number of observations.

6.4.4.5 ITT Population – Study 212

In study 212, the ITT population comprised all patients who were randomly assigned to either the RAPA + CsA or the RAPA group. The mean values for serum creatinine and calculated GFR for the ITT population are shown in Tables 6.4.4.5A and 6.4.4.5B, respectively.

At months 6 and 12, the mean serum creatinine was lower (significantly lower at 6 months) in the CsA-elimination arm (RAPA group) than the corresponding RAPA + CsA group value. At month 12, the mean creatinine values (± SEM) were 176.2 ± 13.2 µmol/L (1.99 ± 0.15 mg/dL)

and 145.4 ± 11.0 µmol/L (1.64 ± 0.12 mg/dL) in the RAPA + CsA and RAPA groups, respectively (p = 0.074).

Mean calculated GFR values were significantly higher at months 6 and 12 in the CsA-elimination arm (RAPA group) than the corresponding RAPA + CsA group values. At month 12, the calculated GFR values were 56.4 ± 2.0 mL/min and 65.3 ± 2.0 mL/min (the RAPA + CsA and RAPA groups, respectively, p = 0.002).

TABLE 6.4.4.5A. OBSERVED MEAN VALUES (± SEM) FOR CREATININE (µmol/L): 12-MONTH DATA (ITT POPULATION): STUDY 212

Time	RAPA + CsA	RAPA	t Test p-Value[a]
Month 6	170.57 ± 9.56 [1.93 ± 0.11][b] (93)[c]	140.80 ± 5.96 [1.59 ± 0.07] (95)	0.009**[d]
Month 12	176.17 ± 13.18 [1.99 ± 0.15] (91)	145.40 ± 10.95 [1.64 ± 0.12] (91)	0.074

RAPA = Rapamune, CsA = cyclosporine, SEM = standard error of the mean, ITT = intent-to-treat.
a: t Test compared the RAPA + CsA group with the RAPA group.
b: Observed mean values ± SEM in mg/dL.
c: Number of observations used for the mean.
d: Statistical significance indicated by **p < 0.01.

TABLE 6.4.4.5B. OBSERVED MEAN VALUES (± SEM) FOR CALCULATED NANKIVELL GFR (mL/min): 12-MONTH DATA (ITT POPULATION): STUDY 212

Time	RAPA + CsA	RAPA	t Test p-Value[a]
Month 6	55.87 ± 1.89 (93)[b]	64.23 ± 1.79 (95)	0.002**[c]
Month 12	56.36 ± 1.98 (91)	65.27 ± 2.01 (91)	0.002**[c]

GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine, SEM = standard error of the mean, ITT = intent-to-treat.
a: t Test compared the RAPA + CsA group with the RAPA group.
b: Number of observations used for the mean.
c: Statistical significance indicated by **p < 0.01.

6.4.5 Efficacy Failure

Table 6.4.5A shows the 12-month efficacy failure data for study 310. Efficacy failure, a secondary endpoint, was defined as the first occurrence of either acute rejection, graft loss, or death. There was no statistically significant difference between the RAPA + CsA group and the RAPA group in the incidence of efficacy failure.

TABLE 6.4.5A. INCIDENCE OF EFFICACY FAILURE BY TREATMENT GROUP AT 12 MONTHS (ITT POPULATION): STUDY 310

Status	RAPA + CsA (n = 215)	RAPA (n = 215)	Nonrandomized (n = 95)	Total (n = 525)
Overall efficacy failure, n (%)	34 (15.8)	48 (22.3)	58 (61.1)	140 (26.7)
Acute rejection	29 (13.5)	43 (20)	29 (30.5)	101 (19.2)
Graft loss	2 (< 1)	1 (< 1)	21 (22.1)	24 (4.6)
Death	3 (1.4)	4 (1.9)	8 (8.4)	15 (2.9)
Fisher's exact p-value[a]	0.110			
Difference in rate,[b] (95% CI)	-6.5 (-13.9 to 0.9)			

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Fisher's exact p-value compares RAPA + CsA with RAPA.
b: Difference is rate of RAPA + CsA – rate of RAPA; a difference > 0 favors RAPA.

Efficacy failure was not a defined endpoint for study 212; therefore, no data for this variable are included in this summary.

6.4.6 Treatment Failure

Table 6.4.6A shows the incidence of treatment failure within the first 12 months following transplantation in study 310. Treatment failure, a secondary endpoint, was defined as the first occurrence of any of the following: discontinuation of study medication use, acute rejection, graft loss, or death.

TABLE 6.4.6A. INCIDENCE OF TREATMENT FAILURE BY TREATMENT GROUP AT 12 MONTHS (ITT POPULATION): STUDY 310

Status	RAPA + CsA (n = 215)	RAPA (n = 215)	Nonrandomized (n = 95)	Total (n = 525)
Overall treatment failure, n (%)	55 (25.6)	80 (37.2)	95 (100)	230 (43.8)
Discontinuation	28 (13)	37 (17.2)	66 (69.5)	131 (25)
Acute rejection	26 (12)	43 (20)	23 (24.2)	92 (17.5)
Graft Loss	0	0	6 (6.3)	6 (1)
Death	1 (< 1)	0	0	1 (< 1)
Fisher's exact p-value[a]	0.012			
Difference in rate,[b] (95% CI)	-11.6 (-20.3 to -2.9)			

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Fisher's exact p-value compares RAPA + CsA with RAPA.
b: Difference is rate of RAPA + CsA – rate of RAPA, a difference > 0 favors RAPA.

In study 310, there was a statistically significant difference in the incidence of treatment failure between the RAPA + CsA and RAPA groups, primarily because of the higher incidences of discontinuation of study medication use and acute rejection in the RAPA group.

Table 6.4.6B shows the incidence of treatment failure for study 212, defined as the first occurrence of any of the following within the first 6 months following transplantation: biopsy-confirmed acute rejection, premature discontinuation of study medication, or conversion to individualized therapy.

TABLE 6.4.6B. INCIDENCE OF TREATMENT FAILURE BY TREATMENT GROUP AT 6 MONTHS (ITT POPULATION): STUDY 212

Assessment	RAPA + CsA (n = 97)	RAPA (n = 100)
Treatment failure, n (%)	29 (29.9)	36 (36.0)
Acute rejection, n (%)	14 (14.4)	18 (18.0)
Discontinuation, n (%)	14 (14.4)	13 (13.0)
Conversion to individualized therapy, n (%)	1 (1.0)	5 (5.0)
95% CI for rate	21.02, 40.04	26.64, 46.21
Difference in rate,[a] (95% CI)	-6.1 (-19.3 to 7.1)	
Fisher's exact p-value	0.369	

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine, CI = confidence interval.
a: Difference is the rate of RAPA + CsA – rate of RAPA; a difference greater than zero favors RAPA.

There was no statistically significant difference in the incidence of treatment failure between the RAPA + CsA and RAPA groups in study 212.

6.4.7 Efficacy Analyses of a Subpopulation of Patients Considered to Be at High Risk for Acute Rejection

Study 310 was not specifically designed or statistically powered to determine the impact of Rapamune treatment in black renal transplant recipients. These patients are considered to have a high degree of immunological risk and thus be at a higher risk for acute rejection episodes.

A total of 8 black patients were included in this study. One (1) patient discontinued study medication use before randomization on day 1 because of renal allograft thrombosis. Five (5) patients were randomly assigned to the RAPA + CsA group, and 2 patients were randomly assigned to the RAPA group. Taken together, there were an insufficient number of black patients enrolled in study 310 to obtain meaningful data specific for this subpopulation.

Study 212 was not specifically designed or statistically powered to determine the impact of sirolimus treatment in black renal transplant patients. These patients are considered to have a high degree of immunological risk and thus be at higher risk for acute rejection episodes. Nineteen percent (19%) of the study 212 population were black, so efficacy data could be analyzed in this subpopulation. These data, presented in the following tables, are from the sNDA submission.

The results of analysis of the rate of biopsy-confirmed acute rejection by race (black versus nonblack) are shown in Table 6.4.7A. At months 2, 6, and 12 following transplantation, higher rates of acute rejection were observed in black patients than in nonblack patients in both the RAPA + CsA and RAPA groups, but the difference was not statistically significant. There were no statistically significant differences in the rate of acute rejection between the RAPA + CsA and RAPA groups for black patients or for nonblack patients.

TABLE 6.4.7A. NUMBER (%) OF PATIENTS WITH BIOPSY-CONFIRMED ACUTE REJECTION BY RACE (BLACK, NONBLACK) AT 2 MONTHS, 6 MONTHS, AND 12 MONTHS AFTER TRANSPLANT (ITT POPULATION): STUDY 212

Time	RAPA + CsA (n = 97)	RAPA (n = 100)	Fisher's Exact p-Value RAPA + CsA vs RAPA	Nonrandomized (n = 49)
Month 2 (≤ 74 days)				
Black, n (%)	4 (22.2)	2 (13.3)	0.665	0 (0)
	n = 18	n = 15		n = 14
Nonblack, n (%)	8 (10.1)	6 (7.1)	0.581	7 (20.0)
	n = 79	n = 85		n = 35
Fisher's exact p-value[a]	0.227	0.344		0.170
Month 6 (≤ 194 days)				
Black, n (%)	4 (22.2)	4 (26.7)	1.000	2 (14.3)
	n = 18	n = 15		n = 14
Nonblack, n (%)	11 (13.9)	14 (16.5)	0.671	7 (20.0)
	n = 79	n = 85		n = 35
Fisher's exact p-value[a]	0.469	0.464		1.000
Month 12 (≤ 379 days)				
Black, n (%)	6 (33.3)	5 (33.3)	1.000	3 (21.4)
	n = 18	n = 15		n = 14
Nonblack, n (%)	12 (15.2)	17 (20.0)	0.540	7 (20.0)
	n = 79	n = 85		n = 35
Fisher's exact p-value[a]	0.095	0.310		1.000

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Fisher's exact p-value compares black with nonblack patients within each treatment group.

Table 6.4.7B shows the observed mean values for serum creatinine, by race (black versus nonblack), in study 212 at various time points. In the RAPA + CsA group, black patients had statistically significantly higher serum creatinine levels than nonblack patients at months 9 and 12. There were statistically significant decreases in serum creatinine values for black patients in the RAPA group (when compared with those in the RAPA + CsA group) at month 12, but creatinine values were only numerically lower for nonblack patients at the same time point.

TABLE 6.4.7B. OBSERVED MEAN VALUES (± SEM) FOR CREATININE (µmol/L) BY RACE (ON-THERAPY POPULATION): STUDY 212

Time	RAPA + CsA (n = 97)	RAPA (n = 100)	t Test p-Value RAPA + CsA vs RAPA	Nonrandomized (n = 49)
Month 1 (week 4)				
Black	174.44 ± 16.78	153.49 ± 13.86	0.371	343.66 ± 101.89
	[1.98 ± 0.19][a]	[1.74 ± 0.16]		[3.89 ± 1.15]
	n = 15	n = 11		n = 8
Nonblack	161.38 ± 11.36	162.12 ± 9.73	0.961	458.90 ± 75.45
	[1.83 ± 0.13]	[1.83 ± 0.11]		[5.19 ± 0.85]
	n = 69	n = 70		n = 13
t Test p-value[b]	0.612	0.733		0.368
Month 2				
Black	172.67 ± 14.30	152.32 ± 13.62	0.316	268.74 ± 77.30
	[1.95 ± 0.16]	[1.72 ± 0.15]		[3.04 ± 0.87]
	n = 15	n = 13		n = 5
Nonblack	146.66 ± 6.83	147.93 ± 11.94	0.926	255.62 ± 35.52
	[1.66 ± 0.08]	[1.67 ± 0.14]		[2.89 ± 0.40]
	n = 61	n = 63		n = 11
t Test p-value[b]	0.097	0.810		0.861
Month 3				
Black	162.07 ± 15.97	147.87 ± 11.75	0.488	218.47 ± 36.48
	[1.83 ± 0.18]	[1.67 ± 0.13]		[2.47 ± 0.41]
	n = 12	n = 11		n = 7
Nonblack	154.00 ± 8.60	140.86 ± 6.00	0.213	211.04 ± 30.74
	[1.74 ± 0.10]	[1.59 ± 0.07]		[2.39 ± 0.38]
	n = 60	n = 60		n = 9
t Test p-value[b]	0.696	0.640		0.878
Month 6				
Black	174.04 ± 15.35	154.70 ± 14.20	0.368	236.47 ± 34.67
	[1.97 ± 0.17]	[1.75 ± 0.16]		[2.68 ± 0.39]
	n = 16	n = 14		n = 8
Nonblack	152.42 ± 7.92	136.05 ± 5.95	0.101	178.63 ± 17.17
	[1.72 ± 0.09]	[1.54 ± 0.07]		[2.02 ± 0.19]
	n = 66	n = 68		n = 15
t Test p-value[b]	0.228	0.205		0.107
Month 9				
Black	183.75 ± 19.40	140.70 ± 12.62	0.086	247.52 ± 39.63
	[2.08 ± 0.22]	[1.59 ± 0.14]		[2.80 ± 0.45]
	n = 14	n = 12		n = 7
Nonblack	148.30 ± 7.20	133.92 ± 8.70	0.207	199.98 ± 20.08
	[1.68 ± 0.08]	[1.51 ± 0.10]		[2.26 ± 0.23]
	n = 58	n = 60		n = 13
t Test p-value[b]	0.046	0.739		0.246

TABLE 6.4.7B. OBSERVED MEAN VALUES (± SEM) FOR CREATININE (µmol/L) BY RACE (ON-THERAPY POPULATION): STUDY 212

Time	RAPA + CsA (n = 97)	RAPA (n = 100)	t Test p-Value RAPA + CsA vs RAPA	Nonrandomized (n = 49)
Month 12				
Black	232.20 ± 34.14 [2.63 ± 0.39] n = 15	136.68 ± 12.08 [1.55 ± 0.14] n = 13	0.017	270.73 ± 51.14 [3.06 ± 0.58] n = 8
Nonblack	154.53 ± 7.24 [1.75 ± 0.08] n = 61	135.15 ± 6.67 [1.53 ± 0.08] n = 64	0.051	191.73 ± 19.39 [2.17 ± 0.22] n = 15
t Test p-value[b]	0.042	0.923		0.182

RAPA = Rapamune, CsA = cyclosporine, SEM = standard error of the mean.
a: Observed mean values ± SEM in mg/dL.
b: t Test p-value compares black with nonblack patients.

Table 6.4.7C shows the observed mean values for calculated Nankivell GFR for the on-therapy patient population in study 212, subdivided by race (black versus nonblack). There were no statistically significant differences between black and nonblack patients in either treatment group (RAPA + CsA or RAPA).

GFRs were also statistically significantly higher in patients in the RAPA group than in the RAPA + CsA group for black patients at months 9 and 12 and for nonblack patients at months 6, 9, and 12.

TABLE 6.4.7C. OBSERVED MEAN VALUES (± SEM) FOR CALCULATED NANKIVELL GFR (mL/min) BY RACE (ON-THERAPY POPULATION): STUDY 212

Time	RAPA + CsA (n = 97)	RAPA (n = 100)	t Test p-Value RAPA + CsA vs RAPA	Nonrandomized (n = 49)
Month 1				
Black	56.45 ± 3.46 n = 15	64.60 ± 4.09 n = 11	0.140	38.43 ± 6.02 n = 8
Nonblack	56.86 ± 2.45 n = 67	56.78 ± 2.30 n = 67	0.980	26.82 ± 4.78 n = 13
t Test p-value[a]	0.940	0.191		0.149
Month 2				
Black	55.89 ± 3.33 n = 15	64.88 ± 3.02 n = 13	0.059	49.56 ± 11.43 n = 5
Nonblack	59.31 ± 2.19 n = 61	61.30 ± 2.31 n = 60	0.534	41.05 ± 3.95 n = 11
t Test p-value[a]	0.471	0.490		0.385

TABLE 6.4.7C. OBSERVED MEAN VALUES (± SEM) FOR CALCULATED NANKIVELL GFR (mL/min) BY RACE (ON-THERAPY POPULATION): STUDY 212

Time	RAPA + CsA (n = 97)	RAPA (n = 100)	t Test p-Value RAPA + CsA vs RAPA	Nonrandomized (n = 49)
Month 3				
Black	58.45 ± 3.75	65.65 ± 3.07	0.156	57.03 ± 8.35
	n = 12	n = 11		n = 7
Nonblack	59.09 ± 2.08	61.62 ± 2.15	0.399	44.00 ± 5.00
	n = 60	n = 60		n = 9
t Test p-value[a]	0.898	0.441		0.181
Month 6				
Black	57.78 ± 3.91	67.71 ± 4.30	0.098	47.00 ± 3.54
	n = 16	n = 14		n = 8
Nonblack	57.31 ± 1.92	64.65 ± 2.13	0.012	52.66 ± 3.86
	n = 66	n = 68		n = 15
t Test p-value[a]	0.914	0.549		0.349
Month 9				
Black	57.32 ± 4.19	71.81 ± 3.42	0.015	48.97 ± 4.40
	n = 14	n = 12		n = 7
Nonblack	58.81 ± 2.16	67.45 ± 2.22	0.006	45.18 ± 4.01
	n = 58	n = 60		n = 13
t Test p-value[a]	0.761	0.405		0.559
Month 12				
Black	50.41 ± 4.31	74.71 ± 3.82	0.0003	48.76 ± 5.65
	n = 15	n = 13		n = 8
Nonblack	57.35 ± 2.29	66.98 ± 2.52	0.006	49.21 ± 4.21
	n = 61	n = 64		n = 15
t Test p-value[a]	0.177	0.191		0.951

GFR = glomerular filtration rate, RAPA = Rapamune, CsA = cyclosporine, SEM = standard error of the mean.
a: t Test p-value compares black with nonblack patients.

Table 6.4.7D shows the rate of treatment failure by race (black versus nonblack). There were no statistically significant differences in the rate of treatment failure between black and nonblack patients within a treatment group or between treatment groups within a race.

TABLE 6.4.7D. NUMBER (%) OF PATIENTS WITH TREATMENT FAILURE BY RACE (ITT POPULATION): STUDY 212

Status	RAPA + CsA (n = 97)	RAPA (n = 100)	Fisher's Exact p-Value RAPA + CsA vs RAPA
Treatment failure, n (%)			
Black	6/18 (33.3)	5/15 (33.3)	1.000
Acute rejection, n	4	4	
Discontinuation, n	2	1	
Conversion to individualized therapy, n	0	0	
Nonblack	23/79 (29.1)	31/85 (36.5)	0.325
Acute rejection, n	10	14	
Discontinuation, n	12	12	
Conversion to individualized therapy, n	1	5	
Fisher's exact p-value[a]	0.778	1.000	

ITT = intent-to-treat, RAPA = Rapamune, CsA = cyclosporine.
a: Compares black with nonblack patients within a treatment group.

6.5 Efficacy Summary and Conclusions

The following conclusions were made for study 310:

- Graft survival was equivalent in the 2 groups: 95.8% in the RAPA + CsA group and 97.2% in the RAPA group at 12 months. The overall graft survival for all patients enrolled in the study was 89.1%.

- Patient survival was similar in the 2 groups at 12 months (97.2% and 98.1% in the RAPA + CsA and RAPA groups, respectively). Patient survival for all patients included in the study was 94.9% at 12 months.

- During the prerandomization period, the overall rate of acute rejection for all patients enrolled in the study was 13.1%.

- The overall acute rejection rate at 12 months for each group was ≤ 20%, and the rates were not significantly different between the RAPA + CsA and RAPA groups (13.5% versus 20.0%, p = 0.093). The 12-month acute rejection rate for the entire study population was 20.2%.

- The elimination of CsA was achieved in a large proportion of the patients (92.6%) randomly assigned to the RAPA group, with only a small increase in the rate of first, biopsy-confirmed acute rejection (4.2% versus 9.8%, p = 0.036; RAPA + CsA group versus RAPA group, respectively) between the time of randomization and 12 months after transplantation.

- Patients in the RAPA group had statistically significantly lower serum creatinine values than those in the RAPA + CsA group at months 6 to 24 after transplantation.

- Elimination of CsA resulted in a significant improvement in calculated GFRs; the mean GFR values at months 6 to 24 for patients randomly assigned to the RAPA group were significantly higher than those for patients randomly assigned to the RAPA + CsA group.

- There was no statistically significant difference in the efficacy failure rate (defined as the first occurrence of either acute rejection, graft loss, or death) at 12 months between the RAPA + CsA and RAPA groups (15.8% and 22.3%, respectively).

- The incidence of treatment failure (defined as the first occurrence of discontinuation of study medication use, acute rejection, graft loss, or death within the first 12 months) was significantly higher in the RAPA group (37.2%) than in the RAPA + CsA group (25.6%, $p = 0.012$), primarily because of slightly higher rates of acute rejection and withdrawals from study medication in the RAPA group.

- The comparison of the RAPA + CsA and RAPA groups for the rates of acute rejection, graft survival, and patient survival for different subpopulations did not establish a clear subgroup of patients who would most likely benefit from the elimination of CsA from the immunosuppressive regimen. However, RAPA-treated patients younger than 50 years or without delayed graft function or with HLA mismatch > 3 had more acute rejections than the corresponding patients in the RAPA + CsA group (data not shown).

In conclusion, the combination of Rapamune, CsA, and corticosteroids for 3 months after transplantation, followed by the progressive elimination of CsA in conjunction with concentration-controlled sirolimus maintenance therapy (RMR) is a safe and effective alternative to long-term CsA-based immunosuppression and can benefit a large proportion of the renal transplant population.

Efficacy analyses in study 212 showed the following:

- Patient and graft survival at 12 months following transplantation were excellent and comparable in the 2 groups.

- The incidence of first biopsy-confirmed acute rejection was comparable in the RAPA + CsA and RAPA groups at 2, 6, and 12 months and during the intervals between months 2 and 6 and months 2 and 12.

- Serum creatinine was statistically significantly lower in the RAPA group than in the RAPA + CsA group at month 12 and numerically lower at months 6 and 9.

- Calculated GFR was statistically significantly higher in the RAPA group than in the RAPA + CsA group at months 6, 9, and 12.

- Measured GFR values were statistically significantly higher in the RAPA group at months 6 and 12 than in the RAPA + CsA group.

- There was no statistically significant difference in the incidence of treatment failure between the RAPA + CsA and RAPA groups. (Treatment failure was defined as the first occurrence of any of the following within the first 6 months after transplantation: biopsy-confirmed acute rejection, premature discontinuation of study medication, or conversion to individualized therapy)

- Although not specifically designed or statistically powered to determine the impact of sirolimus treatment in black patients, analyses of efficacy data in black patients showed the following:

  - At months 2, 6, and 12, higher rates of acute rejection were observed in black patients than in nonblack patients in both the RAPA + CsA and RAPA groups, but the difference was not statistically significant. There were no statistically significant differences in the rate of acute rejection between the RAPA + CsA and RAPA groups for black patients or for nonblack patients.

  - In the RAPA + CsA group, black patients had statistically significantly higher serum creatinine levels than nonblack patients at months 9 and 12. There were statistically significant decreases in serum creatinine values for black patients in the RAPA group (compared with the RAPA + CsA group) at month 12; creatinine values were only numerically lower for nonblack patients at the same time point.

  - There were no statistically significant differences in calculated GFR between black and nonblack patients in either treatment group (RAPA + CsA or RAPA). GFRs were

statistically significantly higher in the RAPA group than in the RAPA + CsA group for black patients at months 9 and 12 and for nonblack patients at months 6, 9, and 12.

- There were no statistically significant differences in the rate of treatment failure between black and nonblack patients within a treatment group (RAPA + CsA or RAPA), or between treatment groups for black patients or for nonblack patients.

In study 212, for the VFE population:

- Patients receiving concentration-controlled sirolimus in whom CsA was eliminated (RAPA group) had a statistically significantly lower mean serum creatinine value at months 6, 9, and 12 than patients receiving standard-dose CsA and fixed-dose Rapamune (RAPA + CsA group).

- Patients in the RAPA group had statistically significantly higher calculated GFR at months 6, 9, and 12 than patients in the RAPA + CsA group.

- Measured GFR was statistically significantly higher in the RAPA group than in the RAPA + CsA group at months 6 and 12.

For all patients who had serum creatinine values at both months 6 and 12 (ITT population) in study 212:

- Serum creatinine was statistically significantly lower at month 6 and numerically lower at month 12 in the RAPA group than in the RAPA + CsA group (140.80 ± 5.96 μmol/L and 170.57 ± 9.56 μmol/L at month 6, respectively).

- Calculated GFR was statistically significantly higher at months 6 and 12 in the RAPA group (RAPA group, 65.27 ± 2.01 mL/min and RAPA + CsA group, 56.36 ± 1.98 mL/min at month 12).

In conclusion, the results from this phase 2 supportive trial demonstrated the safety and efficacy of a regimen utilizing concentration-controlled sirolimus with CsA elimination after 2 months (RAPA). Comparison of RAPA with fixed-dose Rapamune and standard-dose CsA (RAPA + CsA) showed that RAPA was associated with comparable rates of acute rejection at months 2, 6, and 12 while providing a statistically significant improvement in renal function.

7 SAFETY

7.1 Overview

This summary presents safety data from 2 CsA-elimination studies, studies 310 and 212. The designs of the 2 studies, though similar, were distinct, especially with regard to the time of randomization. Therefore, the data from the 2 studies have not been integrated. The safety analyses from the 2 trials are presented together and, where possible, the similarities and differences in the results between the 2 studies are defined. Study 310 is the pivotal study, which was conducted worldwide with a total of 525 renal allograft patients. The supportive study, study 212, was conducted in the United States and Europe with a total of 246 patients.

The data for study 310 include complete 12-month data as well as cumulative data beyond 12 months up to the database cutoff date (03 Jan 2001, at which time all patients who were still participating in the study had received at least 15 months of therapy).

7.2 Patient Populations

The total number of patients included in this summary is presented in Table 7.2A.

TABLE 7.2A. TOTAL NUMBER OF PATIENTS WHOSE DATA WERE EVALUATED FOR SAFETY

Study Subpopulation	n
Pivotal CsA Elimination Study	
Study 310	
Total	525
Nonrandomized	95
RAPA + CsA	215
RAPA	215
Supportive CsA Elimination Study	
Study 212	
Total	246[a]
Nonrandomized	49
RAPA + CsA	97
RAPA	100[a]

RAPA = Rapamune, CsA = cyclosporine.

a: One (1) patient who was enrolled in the RAPA group never received any sirolimus therapy. The data from this patient were included in the demography but not in the safety evaluations.

7.3 Extent of Exposure

7.3.1 Study 310 (Pivotal Study)

A total of 525 patients were enrolled in the study. During the first 3 months of the study when all patients received Rapamune, CsA, and corticosteroids, 95 patients either discontinued study medication before random assignment or were not eligible for randomization; these patients are referred to as the nonrandomized group. At month 3, the remaining 430 patients were randomly assigned to the RAPA + CsA group (n = 215, continued therapy with Rapamune and CsA) or the RAPA group (n = 215, concentration-controlled sirolimus therapy and CsA elimination). All 525 patients enrolled received at least 1 dose of Rapamune and are therefore included in this safety analysis. All patients still participating had received at least 15 months of therapy at the time this summary was prepared.

- At month 18, information for 125 and 112 patients in the RAPA + CsA and RAPA groups, respectively, was available at the time of data cutoff. The mean (± SEM) daily sirolimus doses at month 18 for the RAPA + CsA and RAPA groups were 1.96 (± 0.050 mg; range, 1.00 to 5.00 mg) and 6.35 (± 0.289 mg; range, 1.19 to 15.00 mg), respectively.

- At month 24, information for 27 and 24 patients in the RAPA + CsA and RAPA groups, respectively, was available at the time of the data cutoff. The mean (± SEM) daily sirolimus doses at month 24 for the RAPA + CsA and RAPA groups were 1.85 (± 0.116 mg; range, 1.00 to 4.00 mg) and 5.88 (± 0.580 mg; range, 3.00 to 15.00 mg), respectively.

Figures 7.3.1A and 7.3.1B show that at 12 months the mean sirolimus and CsA trough levels were within the specified concentration ranges as described in the protocol.

FIGURE 7.3.1A. SIROLIMUS TROUGH LEVELS (ng/mL, IMMUNOASSAY)

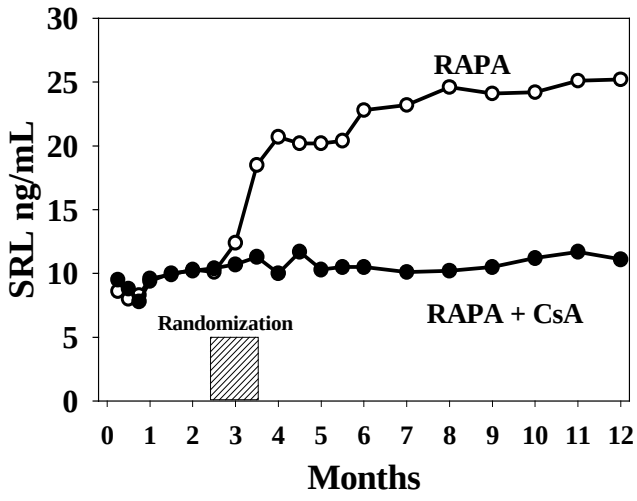
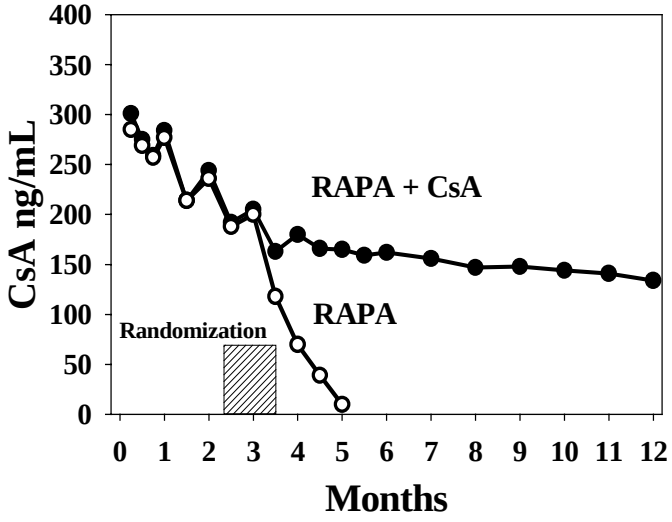


FIGURE 7.3.1B. CsA TROUGH LEVELS (ng/mL, IMMUNOASSAY)



7.3.2 Study 212 (Supportive CsA Elimination Study)

A total of 246 patients were enrolled in the study: 97 in the RAPA + CsA group, 100 in the RAPA group, and 49 in the nonrandomized group. Of these patients, 245 received at least 1 dose of study drug and were included in the safety analysis. At month 12, 79, 78, and 23 patients continued to receive therapy in the RAPA + CsA, RAPA, and nonrandomized groups, respectively. The mean (± SEM) daily sirolimus doses at month 12 for the RAPA + CsA, RAPA, and nonrandomized groups were 1.92 (± 0.055 mg; range, 1.00 to 5.00 mg), 6.56 (± 0.425 mg; range, 1.00 to 28.00 mg), and 3.27 (± 0.407 mg; range, 1.00 to 9.00 mg), respectively.

The status of patients in the RAPA group was as follows:

- At month 6, 82 of the 100 patients who had been randomly assigned were receiving Rapamune therapy (either in the RAPA group or individualized therapy); 19 of these patients took at least 1 dose of CsA during the 6-month time slot.

- At month 12, 17 of the 78 on-therapy patients took at least 1 dose of CsA during the 12-month time slot.

Patient(s) in the RAPA group may have had CsA withdrawn successfully and then reinstituted at a later date.

7.3.3 Overall Summary of Exposure for Studies 310 and 212

In both studies, the mean doses in the RAPA + CsA group were very close to the protocol-mandated dose of 2 mg/day. At month 12, the mean doses in the RAPA group were 7.53 mg/day and 6.56 mg/day in studies 310 and 212, respectively. The difference in the mean daily doses between the 2 studies was due to the different protocol-mandated target trough levels (20 to 30 ng/mL in study 310 and 10 to 20 ng/mL in study 212).

7.4 Concomitant Medications

As is true of transplant patients in general, concomitant medications were commonly administered in both studies. The proportion of patients receiving specific concomitant medications were generally similar in the 2 randomized groups (RAPA + CsA and RAPA) for both studies.

Lipid-lowering agents were frequently used in both studies. Table 7.4A shows the number (and proportion) of patients in each group who received lipid-lowering agents in study 310 before and during Rapamune therapy. Table 7.4B shows the use of lipid-lowering agents for patients on therapy in study 212.

The following observations regarding the randomized groups are noteworthy:

In study 310

- Fifteen percent (15%) and 16% of the patients in the RAPA + CsA and RAPA groups, respectively, received statin therapy before Rapamune treatment. During therapy, 73% of the patients in each of the groups (RAPA + CsA and RAPA) were treated with statins.

- The corresponding values for fibrate use were 3% before therapy for both the RAPA + CsA group and the RAPA group. Fibrate use during therapy was 24% (RAPA + CsA group) and 25% (RAPA group).

- There was no difference in the rate of the use of fibrates or statins between the 2 groups.

In study 212

- Fifty-seven percent (57%) and 65% of the patients in the RAPA + CsA and RAPA groups, respectively, were treated with statins during the first year of therapy. The difference between the RAPA + CsA and RAPA groups was not significant.

- Fibrates were administered to 11% and 8% of the patients in the RAPA + CsA and RAPA groups, respectively. The difference between the RAPA + CsA and RAPA groups was not significant.

TABLE 7.4A. NUMBER (%) OF PATIENTS RECEIVING LIPID-LOWERING AGENTS, BY TREATMENT GROUP (CUMULATIVE DATA): STUDY 310

Medication Classification	RAPA + CsA (n = 215)	RAPA (n = 215)	Fisher's Exact p-Value[a]	Nonrandomized (n = 95)
Before Study				
Any lipid-lowering medication	41 (19)	39 (18)	0.901	28 (29)
Statins (HMGRIs)	32 (15)	35 (16)	0.790	25 (26)
Fibrates	7 (3)	3 (3)	0.337	2 (2)
Ω-3 fatty acids	0	1 (<1)	1.000	0
Other	1 (<1)	0	1.000	1 (1)
Unspecified	1 (<1)	0	1.000	0
During Study				
Any lipid-lowering medication	179 (83)	180 (84)	1.000	37 (39)
Statins (HMGRIs)	156 (73)	158 (73)	0.913	32 (34)
Fibrates	51 (24)	53 (25)	0.910	5 (5)
Ω-3 fatty acids	3 (1)	1 (<1)	0.623	2 (2)
Other	1 (<1)	1 (<1)	1.000	1 (1)
Unspecified	3 (1)	2 (<1)	1.000	1 (1)

RAPA = Rapamune, CsA = cyclosporine, HMGRI = beta-hydroxy, beta-methylglutaryl coenzyme A reductase inhibitor.
a: p-Values are for comparison of RAPA + CsA vs RAPA.

TABLE 7.4B. NUMBER (%) OF PATIENTS RECEIVING STATINS AND FIBRATES BY TREATMENT GROUP WHILE ON THERAPY AT 12 MONTHS: STUDY 212

Lipid-Lowering Drugs	RAPA + CsA (n = 97)	RAPA (n = 99)	Fisher's Exact p-Value RAPA + CsA vs RAPA
Statins (HMGRIs)	55 (57)	64 (65)	0.306
Fibrates	11 (11)	8 (8)	0.477

RAPA = Rapamune, CsA = cyclosporine, HMGRI = beta-hydroxy, beta-methylglutaryl coenzyme A reductase inhibitor.

Tables 7.4C and 7.4D list the specific statins and fibrates, respectively, administered in study 310. Tables 7.4E and 7.4F show the same data for study 212. For the RAPA + CsA and RAPA groups in both studies, the most commonly administered statin was atorvastatin, and the most commonly prescribed fibrate was gemfibrozil.

TABLE 7.4C. NUMBER (%) OF PATIENTS RECEIVING SPECIFIC STATINS BY TREATMENT GROUP (CUMULATIVE DATA): STUDY 310

Treatment Group[a]	Lovastatin	Pravastatin	Simvastatin	Atorvastatin	Cerivastatin	Fluvastatin
RAPA + CsA (n = 215)	5 (2)	26 (12)	37 (17)	104 (48)	10 (5)	14 (7)
RAPA (n = 215)	9 (4)	21 (10)	37 (17)	111 (52)	6 (3)	15 (7)

RAPA = Rapamune, CsA = cyclosporine.
a: Some patients may have received more than 1 statin during therapy.

TABLE 7.4D. NUMBER (%) OF PATIENTS RECEIVING SPECIFIC FIBRATES BY TREATMENT GROUP (CUMULATIVE DATA): STUDY 310

Treatment Group[a]	Clofibrate	Gemfibrozil	Bezafibrate	Fenofibrate
RAPA + CsA (n = 215)	1 (<1)	32 (15)	14 (7)	11 (5)
RAPA (n = 215)	1 (<1)	37 (17)	13 (6)	9 (4)

RAPA = Rapamune, CsA = cyclosporine.
a: Some patients may have received more than 1 fibrate during therapy.

TABLE 7.4E. NUMBER (%) OF PATIENTS RECEIVING SPECIFIC STATINS (12-MONTH DATA): STUDY 212

Treatment Group[a]	Lovastatin	Pravastatin	Simvastatin	Atorvastatin	Cerivastatin	Fluvastatin
RAPA + CsA (n = 97)	1 (1)	13 (13)	11 (11)	46 (47)	3 (3)	1 (1)
RAPA (n = 99)	2 (2)	10 (10)	13 (13)	55 (56)	4 (4)	2 (2)

RAPA = Rapamune, CsA = cyclosporine.
a: Some patients may have received more than 1 statin during therapy.

TABLE 7.4F. NUMBER (%) OF PATIENTS RECEIVING SPECIFIC FIBRATES (12-MONTH DATA): STUDY 212

Treatment Group[a]	Clofibrate	Gemfibrozil	Bezafibrate	Fenofibrate
RAPA + CsA (n = 97)	0	12 (12)	0	0
RAPA (n = 99)	0	7 (7)	0	3 (3)

RAPA = Rapamune, CsA = cyclosporine.
a: Some patients may have received more than 1 fibrate during therapy.

Note that in the RAPA + CsA group in study 212, 11 (11%) patients were treated with fibrates (Table 7.4B), whereas 12 (12%) patients received gemfibrozil (a specific fibrate, Table 7.4F). The discrepancy occurred because Table 7.4B summarizes only the on-therapy data, whereas Table 7.4F summarizes the results from all segments of the study and therefore captures data for patients who were receiving fibrates before starting sirolimus therapy. The same reasoning applies to patients in the RAPA group.

7.5 Adverse Events

Presentation of adverse events in this summary will be limited to treatment-emergent adverse events (TEAEs). TEAEs are defined as events not present at baseline or events present at baseline that worsened during treatment.

7.5.1 TEAEs Excluding Infection and Malignancy

TEAEs were analyzed in the following manner:

- Study 310 prerandomization phase—the baseline was defined as the first day of Rapamune treatment. TEAEs are presented for the nonrandomized group (patients who discontinued treatment before month 3), as well as for patients who subsequently were randomly assigned to the RAPA + CsA and RAPA groups.

- Study 310 postrandomization phase—TEAEs are presented for patients in the RAPA + CsA and RAPA groups randomized at month 3, with the baseline defined as the time of randomization.

- Study 212—TEAEs were analyzed for all patients in the RAPA + CsA and RAPA groups and in the nonrandomized group who received at least 1 dose of study drug. The baseline was defined as the first day of Rapamune treatment.

TEAEs related to infection and malignancy are reported separately. All analyses are based on all reported TEAEs without consideration of the investigator's opinion regarding relationship to treatment. (For selected events, percentages are calculated by using denominators representing either male or female patients, and not the total population.)

In both studies 310 and 212, adverse events and TEAEs were reported for > 96% of the patients in the randomized groups. TEAEs reported at an incidence of ≥ 20% among randomized patients in both studies were hypertension, hyperlipemia, peripheral edema, hypercholesteremia, and creatinine increased. Patients in study 212 also had a high incidence (≥ 20%) of anemia, local reaction to procedure, fever, hypophosphatemia, constipation, headache, thrombocytopenia, diarrhea, dyspnea, albuminuria, nausea, hypokalemia, and pain.

In study 310, the frequencies of the major TEAEs such as hyperlipemia, hypercholesteremia, hypertension, diarrhea, thrombocytopenia, and local reaction to procedure were lower in the postrandomization phase than in the prerandomization phase. This difference probably occurred because the baseline for TEAEs in the postrandomization phase was the patient's status at the time of randomization, and many of these events were evident early in the patient’s posttransplant period (within the first 3 months).

The following noteworthy observations are based on the cumulative postrandomization data for study 310 and the 12-month data for study 212:

- Hypertension and edema were reported more frequently in the RAPA + CsA groups in both studies.

- Thrombocytopenia, hypokalemia, and abnormal liver function tests were reported more frequently in the RAPA groups in both studies.

- TEAEs reported more frequently in the RAPA + CsA group included increased creatinine, CsA toxicity (overdose), and hyperuricemia in study 310 and hypervolemia, dyspnea, and hypomagnesemia in study 212.

- TEAEs reported more frequently in the RAPA group included increased alanine aminotransferase (ALT or SGPT) in study 310 and diarrhea and atrial fibrillation in study 212.

7.5.2 TEAEs Related to Infection

The following observations on infection-related TEAEs are noteworthy for patients in the randomized groups of studies 310 and 212:

- The rates and types of infections reported in both studies were typical of those observed in the renal transplant population in general.

- The most common infections in both studies were urinary tract infection, herpes simplex, upper respiratory infection, pneumonia, and local reaction to procedure.

- In both studies, the rates of the various infections were similar in the randomized groups (the RAPA + CsA and RAPA groups). The 2 exceptions were 1) a higher incidence of herpes zoster in the RAPA + CsA group in study 310 (cumulative postrandomization data: 13 [6.0%] versus 1 [0.5%], the RAPA + CsA and RAPA groups, respectively, p = 0.002) and 2) a higher rate of fungal dermatitis in the RAPA group , study 212 (6 [6.1%] versus 0, the RAPA and RAPA + CsA groups, respectively, p = 0.029).

- The rates of generalized and tissue invasive cytomegalovirus (CMV) infections were low in both studies.

7.5.3 Summary of TEAEs in Studies 310 and 212

The data for patients in the randomized groups showed the following:

- In both studies, TEAEs were reported in > 96% of patients.
- Many CsA-related toxicities were reported less frequently in the CsA-elimination arms (RAPA groups). The specific events are listed below.
  - Hypertension and edema in both studies.
  - Increased creatinine, hyperuricemia, and CsA toxicity in study 310.
  - Hypomagnesemia, hypervolemia, and dyspnea in study 212.
- Thrombocytopenia, hypokalemia, and liver function test abnormalities were more commonly reported in the RAPA groups in both studies, possibly related to the higher sirolimus exposure in these patients. Increased ALT was reported more frequently in the RAPA group in study 310. Diarrhea and atrial fibrillation were reported more frequently in the RAPA group in study 212.
- The rates and types of infection were typical for those seen in the transplant population in general. There was generally no significant difference in the rates of infections between the 2 randomized groups in either study (with the exception of higher rates in study 310 of herpes zoster infection in the RAPA + CsA group and higher rates in study 212 of fungal dermatitis in the RAPA group).

7.6 Deaths, Graft Loss, Malignancy, and Safety-Related Discontinuations

This section includes details on patients who died, had graft loss, or developed malignancy during the study. The patients who discontinued study drug treatment because of an adverse event (regardless of whether the event was considered to be associated with the use of the drug) are also listed.

7.6.1 Deaths

Tables 7.6.1A and 7.6.1B list the patients who died in study 310 (from the time of enrollment through the cutoff date of 03 Jan 2001) and study 212 (final 12-month data). The following information is provided: patient's identification number, age, sex, duration of therapy, study day of death, the reason for discontinuation of study drug, and cause of death.

TABLE 7.6.1A. SUMMARY OF PATIENT DEATHS (CUMULATIVE DATA): STUDY 310

Therapy Group Patient No.	Age (y)	Sex	Days on Therapy	Study Day of Death	Reason for Discontinuation of Study Drug	Cause of Death
RAPA + CsA Group (n = 12)						
310-3216	50	M	167	243	Adverse event	Pulmonary edema
310-3501	53	F	151	152	Adverse event	Cardiac arrest (possible pulmonary embolism, vascular accident)
310-3703	49	M	361	361	Death	Cardiac arrest, diabetic acidosis and hyperkalemia
310-4012	59	M	286	311	Adverse event	Septic shock post-nephrectomy
310-5306	62	M	268	283	Adverse event	Systemic aspergillosis
310-6901	49	M	161	400	Adverse event	Sepsis, pulmonary hemorrhage, cardiac arrest
310-6514	55	M	375	426	Adverse event	Pneumonia, sepsis
310-8103	54	M	422	422	Death	Diabetes complications
310-3215[a]	55	F	767	767	Death	Sudden death
310-3403[a]	42	F	870	870	Death	Cerebral hemorrhage, coma grade III, aggravation of neurological state
310-5503	47	F	541	555	Adverse event	Interstitial pneumonia
310-5805	61	F	205	558	Adverse event	Acute myocardial infarction
RAPA Group (n = 8)						
310-3805	46	M	214	217	Adverse event	Pulmonary aspergillosis
310-5015	60	M	240	354	Adverse event	Cardiac arrest
310-6515	52	F	364	365	Adverse event	Liver malfunction, sepsis
310-6525	68	M	272	317	Adverse event	Sepsis
310-5810[a]	61	M	547	655	Adverse event	Cardiac arrest
310-6522[a]	64	F	656	734	Adverse event	Cardiopulmonary disease, sepsis, pneumonia
310-6804[a]	61	F	119	512	Unsatisfactory response	Cardiac arrest
310-3907	70	F	670	670	Death	Cardiac dysfunction

TABLE 7.6.1A. SUMMARY OF PATIENT DEATHS (CUMULATIVE DATA): STUDY 310

Therapy Group Patient No.	Age (y)	Sex	Days on Therapy	Study Day of Death	Reason for Discontinuation of Study Drug	Cause of Death
Nonrandomized (n = 17)						
310-3008	54	M	11	12	Adverse event	Myocardial infarction following graft hemorrhage
310-3301	64	M	104	410	Adverse event	UTI on a background of metastatic lung cancer
310-4109	54	M	128	143	Adverse event	Pneumonia, sepsis, multiple organ failure
310-4410	72	F	13	14	Adverse event	Peritoneal bleed, acute cardiac failure
310-4811	65	M	5	111	Adverse event	Cardiac infarction 4 days after bypass surgery
310-5204	33	F	32	50	Adverse event	Sudden death
310-5405	47	M	11	405	Adverse event	Pleural infection, hydropneumothorax
310-5808	54	M	44	58	Adverse event	Myocardial infarction
310-6006	40	M	21	29	Adverse event	Pneumonia, cardiovascular complications
310-6201	53	M	5	11	Adverse event	Severe aortic stenosis, cardiac instability
310-6410	48	F	18	361	Adverse event	Pulmonary embolism
310-6501	61	F	54	55	Adverse event	Intracranial bleeding
310-6703	73	M	56	377	Adverse event	Suspected cardiac arrhythmias
310-6801	36	M	21	51	Unsatisfactory response	Hypovolemia and cardiac arrest during surgery
310-7404	53	M	34	54	Adverse event	Disseminated intravascular coagulation, hemorrhage, sepsis
310-7803	62	M	22	23	Adverse event	Myocardial infarction
310-9201	67	F	51	53	Adverse event	Septicemia, multiple organ failure

RAPA = Rapamune, CsA = cyclosporine, UTI = urinary tract infection.

a: Deaths that occurred after data cutoff and are not yet present in database but are included in statistical analysis.

TABLE 7.6.1B. SUMMARY OF PATIENT DEATHS (12-MONTH DATA): STUDY 212

Therapy Group Patient Number	Age (y)	Sex	Days on Therapy	Study Day of Death	Reason for Discontinuation of Study Drug	Cause of Death
RAPA + CsA Group						
(n = 4)						
21202-0211	47	M	1	2	Adverse event	Heart arrest
21206-0607	69	F	350	436	Adverse event	Valvular heart disease
21215-1501	65	F	51	54	Adverse event	Encephalitis
21217-1704[a]	59	M	27	27	Adverse event	Heart arrest
RAPA Group						
(n = 4)						
21202-0207	46	F	263	263	Adverse event	Cardiovascular disorder
21208-0804	50	M	17	18	Adverse event	Lung edema
21208-0831	56	F	315	316	Adverse event	Heart failure, left heart failure
21219-1908	53	M	1	1	Adverse event	Myocardial infarct
Nonrandomized						
(n = 4)						
21218-1812	40	M	22	23	Adverse event	Cerebral ischemia
21224-2406	59	F	4	4	Adverse event	Intracranial hemorrhage
21224-2414	50	M	214	221	Adverse event	Hydrocephalus, cerebral hemorrhage
21224-2419	65	F	3	4	Adverse event	Sepsis

RAPA = Rapamune, CsA = cyclosporine.
a: Patient identified as 21217-0004 in the listings.

In study 310, a total of 37 (7.0%) deaths occurred among the 525 patients enrolled. There were 17 (17.9%) deaths among patients who were not randomly assigned; these deaths were due mainly to early posttransplant complications including cardiovascular events, sepsis, and multiorgan failure. Twelve (12, 5.6%) and 8 (3.7%) of the randomized patients in the RAPA + CsA and RAPA groups, respectively, died. The most common causes were cardiovascular events and infections.

In study 212, the cumulative rate of death for study groups RAPA + CsA, RAPA, and nonrandomized was 4 (4.1%) of 97, 4 (4.0%) of 100, and 4 (8.2%) of 49, respectively. As in the case of study 310, the main causes of death in study 212 were cardiovascular events and infection.

7.6.2 Graft Loss

Table 7.6.2A lists the patients who had graft loss (excluding death with a functioning graft) up to the data entry cutoff date in study 310. Table 7.6.2B provides a similar list for cumulative results up to the data entry cutoff date in study 212. The patients' identification number, age, days on therapy, study day of graft loss, and cause of the graft loss are provided as well.

TABLE 7.6.2A. SUMMARY OF PATIENTS WITH PURE GRAFT LOSS BY GROUP (CUMULATIVE DATA): STUDY 310

Therapy Group Patient No.	Age (y)	Sex	Days on Therapy	Study Day of Graft Loss	Reason for Discontinuation of Study Drug	Cause of Graft Loss
RAPA + CsA Group (n = 9)						
310-3216	50	M	167	210	Sepsis - systemic aspergillosis	Nephrectomy/acute vascular rejection, fibrinoid necrosis
310-4012	59	M	286	301	Perirenal abscess, sepsis	Nephrectomy/perirenal abscess, severe chronic nephropathy
310-4706	44	M	218	242	Loss of graft function	Nephrectomy/chronic hemodialysis, extensive fibrosis, tubular atrophy
310-5305	62	F	225	287	Hyperlipemia, poor renal function	Dialysis/renal dysfunction due to ischemia
310-8503	25	M	294	345	Renal failure	Dialysis/pyelonephritis, graft vascular thrombosis
310-3505	40	M	133	439	Hepatitis B	Nephrectomy/ chronic dialysis, renal dysfunction
310-4302	24	M	431	497	CsA toxicity	Retransplant/ chronic renal dysfunction
310-3903[a]	63	M	392	544	CsA toxicity	Nephrectomy/PTLD
310-4608[a]	34	M	648	869	Renal failure	Dialysis/chronic graft dysfunction
RAPA Group (n = 3)						
310-3822	23	M	221	385	Renal failure	Dialysis/chronic renal insufficiency, relapse of focal segmental glomerular sclerosis
310-5802	59	F	236	294	Elevated creatinine	Dialysis/severe graft dysfunction
310-4001	37	F	474	516	Renal insufficiency	Nephrectomy/chronic rejection, renal dysfunction

TABLE 7.6.2A. SUMMARY OF PATIENTS WITH PURE GRAFT LOSS BY GROUP (CUMULATIVE DATA): STUDY 310

Therapy Group Patient No.	Age (y)	Sex	Days on Therapy	Study Day of Graft Loss	Reason for Discontinuation of Study Drug	Cause of Graft Loss
Nonrandomized (n = 29)						
310-3210	54	F	45	79	Oral *candida albicans*	Nephrectomy/postbiopsy bleeding due to renal angioma
310-3231	25	F	50	51	ATN	Nephrectomy/ATN, hydronephrosis, AV fistula
310-3405	48	F	83	58	Protocol violation	Dialysis/interstitial fibrosis with renal endarteritis
310-3701	47	F	2	2	Vein thrombosis	Nephrectomy/compressive perirenal hematoma and renal vein thrombosis
310-3820	28	M	92	245	Protocol stipulation - creatinine >400 μmol/L	Dialysis/extensive venous thrombosis, chronic graft dysfunction
310-4010	58	M	26	31	Graft loss	Nephrectomy/ATN, graft never began functioning
310-4013	57	M	57	81	Renal dysfunction	Nephrectomy/hydronephrosis, poor graft function
310-4509	24	M	75	131	Renal dysfunction, thrombocytopenia	Dialysis/renal vein obstruction
310-4707	57	F	80	81	Delayed graft function	Nephrectomy/tubulitis, ATN, delayed graft function
310-4807	52	M	17	134	Patient request	Dialysis/severe rejection, ischemia, fibrosis
310-4811	65	M	5	6	Nonfunctioning renal graft	Nephrectomy/suspected thrombosis - no graft circulation
310-5013	27	F	2	16	Thrombocytopenia	Nephrectomy/renal vein thrombosis
310-5204	33	F	32	34	Septic renal hemorrhage	Nephrectomy/renal artery hemorrhage with sepsis
310-5210	48	M	40	41	Perigraft fluid collection	Nephrectomy/perigraft wound infection, septicemia
310-5603	58	F	4	4	Artery thrombosis	Nephrectomy/renal artery thrombosis, ATN
310-5606	39	M	7	7	Vein thrombosis	Nephrectomy/renal vein thrombosis
310-5808	54	M	44	48	Abdominal hemorrhage	Nephrectomy/renal artery and vein thrombosis, diffuse bleeding
310-6414	69	M	108	124	Unsatisfactory response—efficacy	Nephrectomy/tubular damage, chronic graft failure
310-6416	45	M	3	4	Renal graft bleeding	Nephrectomy/rupture of renal graft, bleeding
310-6418	60	F	25	75	Unsatisfactory response—efficacy	Nephrectomy/renal dysfunction, vascular rejection
310-6702	70	M	27	55	Bronchopneumonia	Dialysis/kidney tubular necrosis, renal graft dysfunction

TABLE 7.6.2A. SUMMARY OF PATIENTS WITH PURE GRAFT LOSS BY GROUP (CUMULATIVE DATA): STUDY 310

Therapy Group Patient No.	Age (y)	Sex	Days on Therapy	Study Day of Graft Loss	Reason for Discontinuation of Study Drug	Cause of Graft Loss
310-7404	53	M	34	37	Retroperitoneal bleed	Nephrectomy/retroperitoneal bleed
310-7607	56	M	52	56	CsA toxicity	Dialysis/failed nephrostomy, renal graft dysfunction
310-8310	53	F	35	59	Leukopenia	Nephrectomy/renal artery thrombosis
310-8501	59	M	24	24	Artery thrombosis	Nephrectomy/renal artery thrombosis
310-8605	27	M	28	41	Delayed graft function	Nephrectomy/delayed graft function, severe acute rejection
310-8702	55	M	2	2	Graft thrombosis	Nephrectomy/massive graft venous thrombosis
310-8803	54	F	2	3	Artery thrombosis	Nephrectomy/renal artery thrombosis
310-4805	23	M	102	440	Unsatisfactory response—efficacy	Nephrectomy/chronic renal dysfunction

RAPA = Rapamune, CsA = cyclosporine, PTLD = posttransplant lymphoproliferative disease, ATN = acute tubular necrosis, AV = atrioventricular.
a: Graft losses that occurred after data cutoff and are not yet in database.

TABLE 7.6.2B. SUMMARY OF PATIENTS WITH PURE GRAFT LOSS (12-MONTH DATA): STUDY 212

Therapy Group Patient Number	Age (y)	Sex	Days on Therapy	Study Day of Graft Loss	Reason for Discontinuation of Study Drug	Causes of Graft Loss
RAPA + CsA Group (n = 4)						
21204-0411	50	M	25	190	Unsatisfactory response—efficacy	Acute rejection
21208-0822	37	F	32	169	HUS	HUS
21212-1206	34	M	66	89	Serum creatinine level increased; thrombocytopenia	HUS
21224-2416	67	F	59	1	ATN	ATN
RAPA Group (n = 1)						
21204-0410	34	M	178	350	Unsatisfactory response—efficacy	Acute rejection

TABLE 7.6.2B. SUMMARY OF PATIENTS WITH PURE GRAFT LOSS (12-MONTH DATA): STUDY 212

Therapy Group Patient Number	Age (y)	Sex	Days on Therapy	Study Day of Graft Loss	Reason for Discontinuation of Study Drug	Causes of Graft Loss
Nonrandomized						
(n = 6)						
21204-0408	46	F	4	4	Ischemic transplanted kidney	Ischemic transplanted kidney
21204-0426	42	M	9	10	Thrombosed renal artery and vein transplant kidney	Thrombosed renal artery and vein transplant kidney
21204-0427	65	F	1	1	Thrombosed renal artery	Thrombosed renal artery
21206-0619	23	M	64	4	Thrombocytopenia	ATN/DGF
21214-1409	49	F	63	1	Surgical wound infection; urinary tract infection; vaginitis	Perinephric hematoma, leak ureteral anastomosis
21224-2409	51	M	116	1	ATN	ATN
Impending Graft Loss						
(n = 2)						
RAPA + CsA Group						
21219-1910[a]	45	M	31	339	Unsatisfactory response—efficacy	---
Nonrandomized						
21218-1812[b]	40	M	22	-1	Postanoxic encephalopathy	---

RAPA = Rapamune, CsA = cyclosporine, ATN = acute tubular necrosis, DGF = delayed graft function, HUS = hemolytic uremic syndrome.

a: At the time of the final study evaluation (study day 367), graft loss was impending (patient had been on dialysis for less than 56 days).

b: At the time of death graft loss was impending (patient had been on dialysis for less than 56 days); the allograft never functioned, and patient required dialysis from the day of transplant. Patient died on study day 23.

In study 310, a total of 41 (7.8%) of the 525 patients enrolled had graft loss as of 03 Jan 2001: 29 (30.5%), 9 (4.2%), and 3 (1.4%) in the nonrandomized group and in the RAPA + CsA and RAPA groups, respectively. The main causes of graft loss in the nonrandomized patients were renal thrombosis (artery or vein) and prolonged ATN/DGF. After randomization (until the data cutoff of 03 Jan 2001), 9 patients in the RAPA + CsA group and 3 patients in the RAPA group

had pure graft loss (defined as physical or functional graft loss in a living patient) from a variety of typical causes including acute and chronic rejection and recurrent disease.

In study 212, a total of 11 (4.5%) of 246 patients enrolled had graft loss. The rate of graft loss for the RAPA + CsA, RAPA, and nonrandomized study groups was 4 (4.1%) of 97, 1 (1.0%) of 100, and 6 (12.2%) of 49, respectively (Fisher's exact test p-value for the RAPA + CsA group versus the RAPA group comparison was not significant, p = 0.207). One (1) patient in the RAPA + CsA group (21219-1910) and 1 patient in the nonrandomized group (21218-1812) were classified as having impending graft loss. As in study 310, acute rejection, thrombotic events (including hemolytic uremic syndrome [HUS]), and ATN/DGF were the most common causes of graft loss.

7.6.3 Malignancy

Tables 7.6.3A and 7.6.3B provide lists from the cumulative databases of studies 310 and 212, respectively, of patients in whom malignancies developed. The pertinent patient demographic information is presented as well.

TABLE 7.6.3A. SUMMARY OF PATIENTS WITH MALIGNANCY BY GROUP (CUMULATIVE DATA): STUDY 310

Therapy Group Patient No.	Age (y)	Sex	Days on Therapy	Study Day of Malignancy Diagnosis	Reason for Discontinuation of Study Drug	Type of Malignancy
RAPA + CsA Group (n = 14)						
310-3201[a]	58	M	683	33	Recurrent basal cell carcinoma	Basal and squamous cell carcinoma (pre-study lesions)
310-4302	24	M	430	167	Toxic CsA nephropathy	Basal cell carcinoma
310-5805[b]	60	F	205	204	Lung cancer	Lung cancer
310-7106[a]	47	M	Ongoing	62, 405[c]	Ongoing	Basal and squamous cell carcinoma
310-6514	54	M	376	392	Pancytopenia	Acute myeloid leukemia
310-6520	53	F	394	275	Leukopenia	B cell lymphoma (lymphoma-like reaction)
310-7102	54	M	Ongoing	247, 414[c]	Ongoing	Basal cell carcinoma
310-7402	65	M	Ongoing	233, 514, 574[c]	Ongoing	Basal and squamous cell carcinoma
310-8005	48	F	Ongoing	312	Ongoing	Skin melanoma, basal cell carcinoma
310-3207	63	F	Ongoing	599	Ongoing	Basal cell carcinoma
310-3815	49	M	827	611	Oropharynx cancer[d]	Oropharynx cancer (pre-study lesions)
310-6002	46	M	583	538	Renal cancer of native kidney	Renal cancer of native kidney
310-6506	62	M	Ongoing	665	Ongoing	Prostate cancer
310-7603	41	M	574	461	CsA toxicity	Renal cell carcinoma
RAPA Group (n = 8)						
310-7104[a]	49	M	Ongoing	40, 364, 579[c]	Ongoing	Basal cell carcinoma and squamous cell carcinoma
310-5003	52	F	Ongoing	267	Ongoing	Cervix cancer in situ
310-5015	62	M	240	242	Fever - unknown etiology	Non-Hodgkin B-cell lymphoma
310-7405	48	M	Ongoing	145	Ongoing	Adenomatoid colon polyp low grade
310-6502	36	F	188	599	Hypercholest-eremia, hypertriglyceri-demia	Basal cell carcinoma
310-6805	48	F	138	138	Unsatisfactory response	Basal cell carcinoma on nose
310-7503	37	M	Ongoing	629	Ongoing	Squamous cell carcinoma
310-7101	51	M	Ongoing	533	Ongoing	Squamous cell carcinoma in situ

TABLE 7.6.3A. SUMMARY OF PATIENTS WITH MALIGNANCY BY GROUP (CUMULATIVE DATA): STUDY 310

Therapy Group Patient No.	Age (y)	Sex	Days on Therapy	Study Day of Malignancy Diagnosis	Reason for Discontinuation of Study Drug	Type of Malignancy
Nonrandomized (n = 5)						
310-3301	64	M	104	285	Septicemia	Lung squamous cell carcinoma, liver metastases
310-6601	62	F	6	66, 219, 337[c]	Diffuse abdominal bleeding	Skin carcinoma, angiosarcoma
310-6801	36	M	21	51	Unsatisfactory response	Lymphoproliferative disease
310-6913	56	M	36	24	Unsatisfactory response	Basal cell carcinoma
310-7306	46	M	39	105, 274[c]	Hyperlipemia	Basal cell carcinoma and squamous cell carcinoma

RAPA = Rapamune, CsA = cyclosporine.
Note: A squamous cell carcinoma of the left lung was found in patient 310-3005 (RAPA + CsA) on day 669 (patient discontinued treatment on day 320 because of pneumonia). This event is not yet in the database and is not included in the analysis.
a: Two (2) patients in the RAPA + CsA group (310-3201, 310-7106) and 1 patient in the RAPA group (310-7104) had onset of carcinoma in the prerandomization segment.
b: Patient 310-5805 initially had a positive pathology, but the results of a second biopsy were negative and therefore the patient never received treatment; considered to be a spontaneous regression.
c: Recurrence of disease.
d: Date and reason for discontinuation not yet in database.

TABLE 7.6.3B. SUMMARY OF PATIENTS WITH MALIGNANCY (12-MONTH DATA): STUDY 212

Therapy Group Patient Number	Age	Sex	Days on Therapy	Study Day of Malignancy Diagnosis	Reason for Discontinuation of Study Drug	Type of Malignancy
RAPA + CsA Group						
None						
RAPA Group (n = 4)						
21208-0806	60	M	414	402	Continued in study	Lymphoma-like reaction (non-EBV associated PTLD)[a]
21208-0811	28	F	3	131	Nausea; vomiting; indigestion	Skin carcinoma - squamous cell
21208-0816	52	M	80	176	Unsatisfactory response-efficacy	Skin carcinoma - squamous cell
21217-1705[b]	47	M	361	5	Continued in study	Carcinoma - multifocal renal cell in native kidney
Nonrandomized						
None						

RAPA = Rapamune, CsA = cyclosporine, EBV = Epstein-Barr virus,
PTLD = posttransplant lymphoproliferative disease.
a: Patient 21208-0806: diagnosis of PTLD was never confirmed.
b: Patient identified as 21217-0005 in the listings. Renal carcinoma occurred in the native kidney and was excised.

The crude rate of malignancy was 5.1% (27/525) and 1.6% (4/246) in studies 310 (cumulative data) and 212 (12-month data), respectively. Nonmelanomatous skin cancer was the most commonly reported malignancy in both studies; 1 case of melanoma was reported in study 310 (RAPA + CsA group). Lymphoproliferative disease/leukemia was reported in 4 patients (0.8%) in study 310 and in 1 patient (0.4%) in study 212. The latter patient was noted to have plasma cell infiltrates in the renal allograft that were suggestive of posttransplant lymphoproliferative disease (PTLD); however, a bone marrow examination showed no evidence of malignancy. Tables 7.6.3C and 7.6.3D summarize the malignancies noted in studies 310 and 212, respectively. The overall rates of malignancy and PTLD reported in both studies are consistent with rates reported in the transplant population in general.

TABLE 7.6.3C. SUMMARY OF NUMBER (%) OF PATIENTS IN WHOM MALIGNANCIES WERE REPORTED (CUMULATIVE DATA): STUDY 310

Malignancies[a]	RAPA + CsA (n = 215)	RAPA (n = 215)	p-Value[b]	Nonrandomized (n = 95)	Total (n = 525)
Nonmelanomatous skin cancer	7 (3.3)	5 (2.3)	0.771	3 (3.2)	15 (2.9)
Lymphoma/PTLD/leukemia	2 (< 1)	1 (< 1)	1.000	1 (1.1)	4 (< 1)
Other	5 (2.3)	2 (< 1)	0.449	1 (1.1)	8 (1.5)

RAPA = Rapamune, CsA = cyclosporine, PTLD = posttransplant lymphoproliferative disease.
a: Patients may have reported more than 1 malignancy.
b: Fisher's exact test comparing RAPA + CsA with RAPA.

TABLE 7.6.3D. SUMMARY OF NUMBER (%) OF PATIENTS IN WHOM MALIGNANCIES WERE REPORTED (12 MONTH DATA): STUDY 212

Malignancies[a]	RAPA + CsA (n = 97)	RAPA (n = 100)	p-Value[b]	Nonrandomized (n = 49)	Total (n = 246)
Nonmelanomatous skin cancer	0	2 (2.0)	0.498	0	2 (< 1)
Lymphoma/PTLD/Leukemia	0	1[c] (1.0)	1.000	0	1 (<1)
Other	0	1 (1.0)	1.000	0	1 (< 1)

RAPA = Rapamune, CsA = cyclosporine, PTLD = posttransplant lymphoproliferative disease.
a: Patients may have reported more than 1 malignancy.
b: Fisher's exact test comparing RAPA + CsA with RAPA.
c: A plasma cell infiltrate suggestive of PTLD was diagnosed in patient 21208-0806 on study day 402. The patient's immunosuppressive medication was stopped and the event resolved within 34 days. The diagnosis of PTLD was never confirmed, and the patient remained in and completed the study.

7.6.4 Safety-Related Discontinuations

Table 7.6.4A shows, for study 310, the number of patients who discontinued Rapamune administration through 03 Jan 2001 (cumulative). The primary reasons for discontinuation are also included.

TABLE 7.6.4A. NUMBER (%) OF PATIENTS WHO DISCONTINUED SIROLIMUS USE DURING THE TREATMENT PHASE OF THE STUDY BY PRIMARY REASON AND TREATMENT GROUP (CUMULATIVE DATA): STUDY 310

Reason for Discontinuation	RAPA + CsA (n = 215)[a]	RAPA (n = 215)	p-Value[b]	Nonrandomized (n = 95)
Adverse reaction	42 (20)	43 (20)	1.000	70 (74)
Failed to return	1 (<1)	0	1.000	0
Other	2 (<1)	1 (<1)	1.000	2 (2)
Other nonmedical event	1 (< 1)	0	1.000	1 (1)
Patient request	3 (1)	6 (3)	0.503	4 (4)
Protocol stipulation	0	0	-	2 (2)
Protocol violation	1 (< 1)	4 (2)	0.372	4 (4)
Unsatisfactory response - efficacy	9 (4)	11 (5)	0.446	12 (13)
Total	59 (27)	65 (30)	0.595	95 (100)

RAPA = Rapamune, CsA = cyclosporine.

a. Includes patient 310-3703 whose reason for discontinuation was incorrectly reported as patient death instead of adverse event: cardiac arrest (see errata in CSR-40858).

b. Fisher's exact test comparing RAPA + CsA with RAPA.

Table 7.6.4B shows, for study 212, the number of patients who discontinued Rapamune administration (12 month data) and the primary reasons for the discontinuation.

TABLE 7.6.4B. NUMBER (%) OF PATIENTS WHO DISCONTINUED SIROLIMUS USE DURING THE TREATMENT PHASE OF THE STUDY BY PRIMARY REASON AND BY TREATMENT GROUP (12-MONTH DATA): STUDY 212

Reason for Discontinuation	RAPA + CsA (n = 97)	RAPA (n = 99)	Fisher's Exact p-Value[a]	Nonrandomized (n = 49)
Adverse reaction	12 (12)	12 (12.0)	1.000	20 (41)
Failed to return[b]	0	2 (2)	0.497	2 (4)
Other nonmedical event[c]	0	0	1.000	1 (2.0)
Patient request	3 (3)	7 (7)	0.331	1 (2)
Protocol violation	0	1 (1)	1.000	1 (2)
Unsatisfactory response - efficacy	5 (5)	4 (4)	0.746	3 (6)
Total	20 (21)	25 (25)	0.499	28 (57)

RAPA = Rapamune, CsA = cyclosporine.

a: Fisher's exact test compares RAPA + CsA with RAPA.

b: Two (2) patients in the RAPA group and 1 patient in the nonrandomized group completed the treatment phase but failed to return for a follow-up visit.

c: One (1) patient in the nonrandomized group completed the treatment phase but did not return for a follow-up visit.

The nonrandomized group for study 310 is defined as those patients who either discontinued therapy before randomization or were not eligible for randomization. The rate of "discontinuation" in this group is therefore, by definition, 100%. Adverse events were the main cause of discontinuation. The adverse events that most frequently (≥ 4%) led to discontinuation

(arranged in descending order of frequency of occurrence) for the nonrandomized patients were thrombotic thrombocytopenic purpura (8.4%), local reaction to procedure (7.4%), thrombocytopenia (6.3%), hypercholesteremia (5.3%) and hyperlipemia (5.3%), kidney tubular necrosis (5.3%), and vascular thrombosis of the allograft (4.2%).

Table 7.6.4C presents a tabulation of the adverse events causing withdrawal of patients in the randomized groups (the RAPA + CsA and RAPA groups) of study 310.

TABLE 7.6.4C. NUMBER (%) OF PATIENTS IN WHOM ADVERSE EVENTS LED TO WITHDRAWAL FROM STUDY: GROUPS RAPA + CsA AND RAPA (CUMULATIVE DATA)—STUDY 310

Body System[a] Adverse Event	RAPA + CsA (n = 215)	RAPA (n = 215)	Total (n = 430)	Fisher's Exact p-Value[b]
Any adverse reaction	46[c](21.4)	45[c](20.9)	91 (21.1)	1.000
Body as a whole				
Carcinoma	1 (0.5)	0	1 (0.2)	1.000
Face edema	0	1 (0.5)	1 (0.2)	1.000
Fever	1 (0.5)	2 (0.9)	3 (0.7)	1.000
Generalized edema	1 (0.5)	0	1 (0.2)	1.000
Infection	3 (1.4)	2 (0.9)	5 (1.2)	1.000
Lab test abnormal	0	2 (0.9)	2 (0.5)	0.499
Overdose	7 (3.3)	0	7 (1.6)	0.015*
Pain	0	1 (0.5)	1 (0.2)	1.000
Peritonitis	1 (0.5)	0	1 (0.2)	1.000
Sepsis	2 (0.9)	1 (0.5)	3 (0.7)	1.000
Cardiovascular system				
Heart arrest	3 (1.4)	0	3 (0.7)	0.248
Hypertension	1 (0.5)	0	1 (0.2)	1.000
Myocardial infarct	1 (0.5)	0	1 (0.2)	1.000
Vasodilatation	1 (0.5)	0	1 (0.2)	1.000
Digestive system				
Diarrhea	1 (0.5)	1 (0.5)	2 (0.5)	1.000
Gamma glutamyl transpeptidase increased	0	1 (0.5)	1 (0.2)	1.000
Gum hyperplasia	1 (0.5)	0	1 (0.2)	1.000
Hepatitis	1 (0.5)	1 (0.5)	2 (0.5)	1.000
Liver damage	0	1 (0.5)	1 (0.2)	1.000
Liver function tests abnormal	0	3 (1.4)	3 (0.7)	0.248
Oral moniliasis	1 (0.5)	0	1 (0.2)	1.000
Pancreatitis	0	1 (0.5)	1 (0.2)	1.000
Endocrine system				
Diabetes mellitus	1 (0.5)	0	1 (0.2)	1.000
Hemic and lymphatic system				
Anemia	1 (0.5)	2 (0.9)	3 (0.7)	1.000
Leukopenia	1 (0.5)	0	1 (0.2)	1.000
Pancytopenia	1 (0.5)	1 (0.5)	2 (0.5)	1.000
Thrombotic thrombocytopenic purpura	1 (0.5)	0	1 (0.2)	1.000

TABLE 7.6.4C. NUMBER (%) OF PATIENTS IN WHOM ADVERSE EVENTS LED TO WITHDRAWAL FROM STUDY: GROUPS RAPA + CsA AND RAPA (CUMULATIVE DATA)—STUDY 310

Body System[a] Adverse Event	RAPA + CsA (n = 215)	RAPA (n = 215)	Total (n = 430)	Fisher's Exact p-Value[b]
Metabolic and nutritional				
Acidosis	1 (0.5)	0	1 (0.2)	1.000
Alkaline phosphatase increased	0	1 (0.5)	1 (0.2)	1.000
ALT increased	0	1 (0.5)	1 (0.2)	1.000
AST increased	0	1 (0.5)	1 (0.2)	1.000
Creatinine increased	4 (1.9)	4 (1.9)	8 (1.9)	1.000
Glucose tolerance decreased	0	1 (0.5)	1 (0.2)	1.000
Gout	1 (0.5)	0	1 (0.2)	1.000
Hypercholesteremia	3 (1.4)	6 (2.8)	9 (2.1)	0.503
Hyperkalemia	1 (0.5)	0	1 (0.2)	1.000
Hyperlipemia	4 (1.9)	5 (2.3)	9 (2.1)	1.000
Peripheral edema	1 (0.5)	0	1 (0.2)	1.000
Musculoskeletal system				
Arthralgia	1 (0.5)	1 (0.5)	2 (0.5)	1.000
Arthritis	1 (0.5)	0	1 (0.2)	1.000
Bone necrosis	0	1 (0.5)	1 (0.2)	1.000
Bone pain	0	1 (0.5)	1 (0.2)	1.000
Myalgia	0	1 (0.5)	1 (0.2)	1.000
Rhabdomyolysis	1 (0.5)	0	1 (0.2)	1.000
Nervous system				
Abnormal dreams	1 (0.5)	0	1 (0.2)	1.000
Neuritis	1 (0.5)	0	1 (0.2)	1.000
Tremor	1 (0.5)	0	1 (0.2)	1.000
Respiratory system				
Carcinoma of lung	1 (0.5)	0	1 (0.2)	1.000
Cough increased	0	1 (0.5)	1 (0.2)	1.000
Dyspnea	2 (0.9)	0	2 (0.5)	0.499
Pneumonia	3 (1.4)	3 (1.4)	6 (1.4)	1.000
Pulmonary mycosis	0	1 (0.5)	1 (0.2)	1.000
Sinusitis	1 (0.5)	0	1 (0.2)	1.000
Skin and Appendages				
Alopecia	0	1 (0.5)	1 (0.2)	1.000
Hirsutism	2 (0.9)	0	2 (0.5)	0.499
Psoriasis	0	1 (0.5)	1 (0.2)	1.000
Skin carcinoma	1 (0.5)	0	1 (0.2)	1.000
Special senses				
Eye disorder	0	1 (0.5)	1 (0.2)	1.000

TABLE 7.6.4C. NUMBER (%) OF PATIENTS IN WHOM ADVERSE EVENTS LED TO WITHDRAWAL FROM STUDY: GROUPS RAPA + CsA AND RAPA (CUMULATIVE DATA)—STUDY 310

Body System[a] Adverse Event	RAPA + CsA (n = 215)	RAPA (n = 215)	Total (n = 430)	Fisher's Exact p-Value[b]
Urogenital system				
Acute kidney failure	0	1 (0.5)	1 (0.2)	1.000
Kidney abscess	1 (0.5)	0	1 (0.2)	1.000
Kidney failure	1 (0.5)	0	1 (0.2)	1.000
Kidney function abnormal	4 (1.9)	2 (0.9)	6 (1.4)	0.685
Nephritis	0	1 (0.5)	1 (0.2)	1.000
Toxic nephropathy	1 (0.5)	0	1 (0.2)	1.000
Uremia	1 (0.5)	2 (0.9)	3 (0.7)	1.000
Adverse event assoc. w. misc. factors				
Local reaction to procedure	1 (0.5)	0	1 (0.2)	1.000

RAPA = Rapamune, CsA = cyclosporine, ALT = alanine aminotransferase (SGPT), AST = aspartate aminotransferase (SGOT).
a: For selected events, percentages are calculated by using denominators representing either male or female patients, not the total population.
b: p-Value: *p ≤ 0.05.
c: These numbers differ from those reported in Table 7.6.4A because this table includes patients for whom an adverse event was either the primary or the secondary reason for discontinuation.

A tabulation of the adverse events that led to withdrawal from study 212 in the randomized groups (the RAPA + CsA and RAPA groups), obtained from the 12-month database, is provided in Table 7.6.4D.

TABLE 7.6.4D. NUMBER (%) OF PATIENTS IN WHOM ADVERSE EVENTS LED TO WITHDRAWAL FROM STUDY: GROUPS RAPA + CsA AND RAPA—STUDY 212

Body System[a] Adverse Event	RAPA + CsA (n = 97)	RAPA (n = 99)	Total (n = 196)	Fisher's Exact Test p-Value
Any adverse reaction	13[b] (13.4)	12[b] (12.1)	25 (12.8)	0.833
Body as a whole				
Asthenia	1 (1.0)	1 (1.0)	2 (1.0)	1.000
Peritonitis	0	1 (1.0)	1 (0.5)	1.000
Cardiovascular system				
Cardiovascular disorder	0	1 (1.0)	1 (0.5)	1.000
Heart arrest	2 (2.1)	0	2 (1.0)	0.244
Heart failure	0	1 (1.0)	1 (0.5)	1.000
Left heart failure	0	1 (1.0)	1 (0.5)	1.000
Myocardial infarct	1 (1.0)	1 (1.0)	2 (1.0)	1.000

TABLE 7.6.4D. NUMBER (%) OF PATIENTS IN WHOM ADVERSE EVENTS LED TO WITHDRAWAL FROM STUDY: GROUPS RAPA + CsA AND RAPA—STUDY 212

Body System[a] Adverse Event	RAPA + CsA (n = 97)	RAPA (n = 99)	Total (n = 196)	Fisher's Exact Test p-Value
Digestive system				
Diarrhea	0	1 (1.0)	1 (0.5)	1.000
Dyspepsia	0	1 (1.0)	1 (0.5)	1.000
Enteritis	0	1 (1.0)	1 (0.5)	1.000
Nausea	1 (1.0)	1 (1.0)	2 (1.0)	1.000
Vomiting	1 (1.0)	1 (1.0)	2 (1.0)	1.000
Hemic and lymphatic system				
Anemia	0	1 (1.0)	1 (0.5)	1.000
Thrombocytopenia	2 (2.1)	1 (1.0)	3 (1.5)	0.619
Thrombotic thrombocytopenic purpura	2 (2.1)	0	2 (1.0)	0.244
Metabolic and nutritional				
Creatinine increased	2 (2.1)	0	2 (1.0)	0.244
Hyperlipemia	0	1 (1.0)	1 (0.5)	1.000
Musculoskeletal system				
Myopathy	1 (1.0)	0	1 (0.5)	0.495
Nervous system				
Encephalitis	1 (1.0)	0	1 (0.5)	0.495
Neuropathy	0	1 (1.0)	1 (0.5)	1.000
Respiratory system				
Lung edema	0	1 (1.0)	1 (0.5)	1.000
Skin and appendages				
Hirsutism	2 (2.1)	0	2 (1.0)	0.244
Urogenital system				
Kidney tubular necrosis	1 (1.0)	0	1 (0.5)	0.495
Toxic nephropathy	1 (1.0)	0	1 (0.5)	0.495
Adverse event assoc. w. misc. factors				
Local reaction to procedure	0	1 (1.0)	1 (0.5)	1.000

RAPA = Rapamune, CsA = cyclosporine.

a: For selected events, percentages are calculated by using denominators representing either male or female patients, and not the total population.

b: These numbers differ from those reported in Table 7.6.4B because this table includes patients for whom an adverse event was either the primary or the secondary reason for discontinuation.

Adverse events were the main cause of discontinuation in the nonrandomized patients in study 212. The adverse events that most frequently (≥ 4%) led to discontinuation were thrombocytopenia (6.1%), kidney tubular necrosis (6.1%), vaginitis (5.3%), and leukopenia (4.1%).

In both studies, the causes of discontinuation in the randomized groups were similar in the 2 groups except for a significantly higher rate of discontinuation due to CsA toxicity (overdose) in the RAPA + CsA group of study 310 (3.3% versus 0%, the RAPA + CsA and RAPA groups, respectively, p = 0.015). There were no predominant causes of discontinuation in either treatment group.

7.6.4.1 Discontinuations Due to Pneumopathy: Study 310

A list of patients who discontinued treatment in study 310 because of pneumonitis, either infectious or with other etiologies, is provided in Table 7.6.4.1A. The majority of the patients had pneumonia diagnosed or had culture confirmation of an infectious etiology. Patient 310-5005 (RAPA group) was admitted with fever and pulmonary infiltrates. An infectious etiology could not be ascertained. The patient's symptoms and x-ray findings resolved after 2 weeks of antibiotic therapy and discontinuation of Rapamune treatment. In 2 patients, not included in this table, a pulmonary process may have contributed to study medication discontinuation. These patients are described below:

- Patient 310-3803 (RAPA group)—This patient began Rapamune therapy on 10 Sep 1998. He was admitted on 04 Jun 1999 with fever and "interstitial pneumonia." No infectious agent was isolated. He was treated with a 2-week course of antibiotics without resolution. Rapamune treatment was discontinued on 10 Jun 1999. Two (2) days later, the patient began a 6-month course of antituberculous therapy. A subsequent x-ray film within 3 months was normal.

- Patient 310-5101 (RAPA group)—This patient discontinued Rapamune because of hyperlipemia; however, interstitial pneumonia was listed as a secondary cause of discontinuation. The patient presented with fever, cough, and "pneumonia" on x-ray film. He recovered after antibiotic therapy and Rapamune discontinuation.

TABLE 7.6.4.1A. SUMMARY OF PATIENTS WHO DISCONTINUED TREATMENT BECAUSE OF PNEUMOPATHY: STUDY 310

Therapy Group Patient No. (Age, y)	Days on Therapy	Duration of Event (days)	Type of Pneumopathy
RAPA + CsA Group			
310-3005 (60)	230	24	Suspected EBV infection. Patient recovered.[a]
310-3007 (27)	211	49	CMV pneumonitis. Patient recovered.[a]
310-3306 (53)	119	5	Left upper lobe pneumonia later diagnosed as CMV. Patient recovered.[a]
310-5306 (63)	268	15	Pulmonary and disseminated *Aspergillus*. Patient died.
310-5303 (45)	539	17	Interstitial pneumonia. Patient died.[b]
RAPA Group			
310-3805 (46)	214	6	Bilateral *Aspergillus* pneumopathy. Patient died.
310-5005 (57)	319	14	Pulmonary infiltrates without pathogen. Patient recovered.[a]
310-5307 (71)	276	18	Pulmonary *Aspergillus*. Patient recovered.[a]
310-8007 (46)	453	25	Pneumonia, *Staphylococcus aureus*. Patient recovered.[a]
310-9303 (59)	470	45	Bilateral pneumopathy, pulmonary infiltrates. Patient recovered.[a]
Nonrandomized			
310-6006 (40)	21	8	Interstitial pneumonia with no infectious pathogens identified. Patient died.
310-6604 (58)	40	10	Pneumonia shown by imaging. Patient recovered.[a]
310-6702 (69)	28	23	Bronchopneumonia shown by imaging. Patient recovered.[a]

RAPA = Rapamune, CsA = cyclosporine, EBV = Epstein-Barr virus, CMV = cytomegalovirus.
a: Recovered with antibiotic therapy.
b: Event not drug related; due to postsurgical complications.

7.6.5 Overall Summary of Deaths, Graft Loss, Malignancy, and Safety-Related Discontinuations for Studies 310 and 212

- In both studies, the overall rates of death and graft loss were similar in the randomized groups (the RAPA + CsA and RAPA groups). The nonrandomized groups had higher rates of death and graft loss, which reflected the fact that many of these patients had risk factors associated with decreased patient and graft survival.

- The overall rate of malignancy was low: 1.6% (12-month data) and 5.1% (cumulative data) in studies 212 and 310, respectively. There were 4 cases of lymphoma/PTLD/leukemia in study 310. There was 1 case of PTLD in study 212; however, the diagnosis of PTLD was never confirmed, and the patient remained in and completed the study.

The rate of discontinuation at 1 year in study 212 was similar in the 2 treatment groups (21% and 25%, the RAPA + CsA and RAPA groups, respectively). The rate of discontinuation in study 310 was numerically, but not statistically, higher in the RAPA group (27% versus 30%, the RAPA + CsA and RAPA groups, respectively). There was no predominant reason for the higher discontinuation rate in the RAPA group.

7.7 Clinical Laboratory Evaluations in Clinical Trials

Laboratory values of clinical importance in the transplant population are presented in the sections that follow. The following statements pertain to these laboratory values, unless otherwise specified:

- Whenever observed means are presented, the values of all patients who were receiving study medication and provided a value at the corresponding time point were used to determine the mean value.

- Whenever adjusted means are presented, the values of those patients who had a baseline value, were receiving study medication, and provided a value at the corresponding time point were used to determine the adjusted mean value.

- Whenever the proportion of patients within a toxicity grade is presented (section 7.7.4, Serum Lipid Tests), the values of all patients who were taking the study drug and who provided a value at the corresponding time point were used. Therefore, the numbers of patients in these tables differ from those used to determine the adjusted mean value.

In study 310:

- The observed laboratory values were used to calculate the mean values for all groups.

- The analysis at month 3 represents an ANCOVA (comparison between the RAPA + CsA and RAPA groups) for those patients who were randomly assigned before the month 3 visit; the last prerandomization value was used as baseline. Because month 3 was the time of randomization, no statistical comparisons are made between the RAPA + CsA and RAPA groups values at months 1 and 2.

- No statistical comparisons were made by using the values from the nonrandomized group.

In study 212:

- Observed values are presented for all 3 groups for tests of renal function (serum creatinine, calculated GFR, measured GFR, and blood urea nitrogen [BUN]). The 2 group t-test was used to make the comparisons between the RAPA + CsA and RAPA groups.

- For all other laboratory values, the adjusted mean values are presented for the RAPA + CsA and RAPA groups and the observed mean values are presented for the nonrandomized group. The comparison between the RAPA + CsA and RAPA groups represents an ANCOVA using the baseline value as covariate.

- No statistical comparisons were made using the nonrandomized group values.

7.7.1 Renal Function Tests

The results and analyses of renal function tests are presented in section 6.4.4. In summary:

- The results from studies 310 and 212 were consistent. Patients in the CsA-elimination arm (RAPA group) had significantly better renal function than patients in whom CsA was maintained (RAPA + CsA group), as noted by significantly lower serum creatinine and significantly higher calculated GFR values.

- The above finding was confirmed in study 212 with measured GFRs, which were significantly higher in the RAPA group at months 6 and 12.

- A subpopulation analysis in study 310 showed a beneficial effect of CsA elimination on renal function in high-risk patients.

7.7.2 Serum Chemistry Tests

7.7.2.1 Glucose

In study 310, the only statistically significant differences in the adjusted mean serum glucose values were seen at months 12 and 15, when the mean levels in the RAPA group were significantly higher than those in the RAPA + CsA group, but the differences were not clinically meaningful. There were no significant differences between the RAPA + CsA group and the RAPA group at any time point in study 212.

7.7.2.2 Urea and Urea Nitrogen

In study 310, the mean serum urea values for the RAPA group were significantly lower than those for the RAPA + CsA group at months 6 to 24. In study 212, BUN values were numerically lower from month 1 to 3 and significantly lower from months 6 through 12 in the RAPA group than in the RAPA + CsA group. The lower urea and BUN values in the RAPA group are likely a reflection of the better GFR values in these patients.

7.7.2.3 Magnesium

In both studies 310 and 212, the adjusted mean serum magnesium levels were significantly higher in the RAPA group than the corresponding values in the RAPA + CsA group at months 6 to 24 (study 310) and months 6 to 12 (study 212). Hypomagnesemia is a well-known side effect of CsA therapy.

7.7.2.4 Potassium

The mean potassium levels were significantly lower in the RAPA group than the corresponding values in the RAPA + CsA group at months 6 to 24 for study 310 and months 6, 9, and 12 for study 212. CsA is known to cause hyperkalemia; the absence of this effect along with the higher Rapamune exposure in the RAPA group may explain the lower potassium values in these patients.

7.7.2.5 Uric Acid

The adjusted mean serum uric acid values were significantly lower in the RAPA group in both studies for most time points. Hyperuricemia has been well described with CsA therapy; this, along with the higher Rapamune exposure in the RAPA group, likely accounted for the observed differences.

7.7.2.6 Phosphorus

In general, patients in the RAPA group had lower mean phosphorus levels than those in the RAPA + CsA group. In comparison with the RAPA + CsA group, the differences in phosphorus levels between the groups reached statistical significance in study 310 at months 6, 9, 12, 21, and 24, and in study 212 at month 12. The clinical importance of these findings is uncertain.

7.7.2.7 Overall Summary of Serum Chemistry Tests for Studies 310 and 212

In summary, a comparison between the RAPA + CsA group and the RAPA group showed the following for the RAPA group:

- Lower values for potassium and uric acid over time. These findings are consistent with both the absence of CsA effect and greater sirolimus exposure in the RAPA group.
- Higher magnesium values over time, consistent with association of CsA with magnesium wasting.
- Lower urea and BUN values over time, likely due to the higher GFR values in the RAPA group.
- Generally lower mean phosphorus levels, the clinical importance of which is uncertain.
- There were no statistically significant differences in the adjusted mean serum glucose values between the RAPA + CsA group and the RAPA group at any time point in study 212 and only at months 12 and 15 in study 310. At those times the mean levels in the RAPA group were significantly higher in the RAPA + CsA group, but the differences were not clinically meaningful.

7.7.3 Hematologic Values

7.7.3.1 Hemoglobin

Hemoglobin levels increased in all groups from months 1 through 12 and remained at about the level found at this time point up to month 24 (for study 310). The mean hemoglobin values were similar in the RAPA + CsA and RAPA groups in both studies. Exceptions occurred in study 310 for the readings at months 6 and 9 (when the RAPA group values were significantly lower) and at months 18, 21, and 24 (when the RAPA group values were significantly higher). These observed differences are likely of little clinical importance. It should be noted that in study 310, only 1 patient in the RAPA + CsA group and 2 patients in the RAPA group discontinued study medication because of anemia. In study 212, 1 patient in the RAPA group discontinued treatment because of anemia.

7.7.3.2 White Blood Cells

In general, the white blood cell (WBC) counts were similar in the RAPA + CsA and RAPA groups in both studies.

7.7.3.3 Platelets

In both studies, the platelet counts were generally lower in the RAPA group, likely reflecting the greater Rapamune exposure in these patients. The comparison between the RAPA + CsA and RAPA groups reached statistical significance in study 310 at months 6, 9, 15, and 18 and at month 1 in study 212. The mean platelet values in all groups were generally within the normal range at all time points.

7.7.3.4 Overall Summary of Hematologic Values for Studies 310 and 212

In both studies

- The mean hemoglobin and WBC values were similar in the RAPA + CsA and RAPA groups. The isolated significant differences noted in study 310 are likely not clinically important.
- Mean platelet counts were generally lower in the RAPA group, but generally remained within the normal range.
- No long-term effect on hematopoiesis was observed.

7.7.4 Serum Lipid Tests

7.7.4.1 Cholesterol

In both studies

- The mean cholesterol levels in the RAPA + CsA and RAPA groups peaked during months 2 or 3 and improved to lower values thereafter.
- The mean cholesterol levels in the RAPA + CsA and RAPA groups were generally similar. It is noteworthy that in the RAPA group the Rapamune dose was > 3-fold higher and the sirolimus concentration was > 2-fold higher than the corresponding values in the RAPA + CsA group.

The numbers of patients with clinically important elevations of serum cholesterol values were identified by applying the National Cholesterol Education Program Adult Treatment Panel II guidelines.[28] These guidelines grade the severity of the serum cholesterol value for each patient at months 1, 3, 6, 12, 18, and 24 (study 212 data are available only to month 12). The mean of all the reported values at each corresponding time period was used for study 212, and the last available value of each corresponding time period was used for study 310. The proportions of patients with high (> 6.19 mmol/L, or > 240 mg/dL) and normal-borderline (≤ 6.19 mmol/L, or ≤ 240 mg/dL) cholesterol values at various intervals are presented in Tables 7.7.4.1A and 7.7.4.1B for studies 310 and 212, respectively.

In both studies, the percent of patients with cholesterol levels > 6.19 mmol/L (> 240 mg/dL) was similar in the 2 treatment groups and decreased from month 1 to month 12; these numbers remained stable until month 24 in study 310 patients. In study 310, 3 patients in the RAPA + CsA group and 6 patients in the RAPA group discontinued treatment for hypercholesteremia by the data cutoff date of 03 Jan 2001.

TABLE 7.7.4.1A. DISTRIBUTION OF PATIENTS BY FASTING SERUM CHOLESTEROL VALUE: NUMBER (%) OF PATIENTS: STUDY 310

Time Point Treatment Group	Normal-Borderline (≤ 6.19 mmol/L) [≤ 240 mg/dL]	High (> 6.19 mmol/L) [> 240 mg/dL]
Month 1		
RAPA + CsA (n = 173)	49 (28.3)[a]	124 (71.7)
RAPA (n = 180)	61 (33.9)	119 (66.1)
Month 3		
RAPA + CsA (n = 162)	60 (37.0)	102 (63.0)
RAPA (n = 161)	50 (31.1)	111 (68.9)
Month 6		
RAPA + CsA (n = 154)	77 (50.0)	77 (50.0)
RAPA (n = 147)	64 (43.5)	83 (56.5)
Month 12		
RAPA + CsA (n = 156)	92 (59.0)	64 (41.0)
RAPA (n = 142)	77 (54.2)	65 (45.8)
Month 18		
RAPA + CsA (n = 92)	59 (64.1)	33 (35.9)
RAPA (n = 91)	49 (53.9)	42 (46.1)
Month 24		
RAPA + CsA (n = 20)	11 (55.0)	9 (45.0)
RAPA (n = 20)	11 (55.0)	9 (45.0)

RAPA = Rapamune, CsA = cyclosporine.

a: All Mantel-Haenszel chi-square p-values for RAPA + CsA vs RAPA were not significant ($p > 0.05$).

TABLE 7.7.4.1B. DISTRIBUTION OF PATIENTS BY SEVERITY OF FASTING SERUM CHOLESTEROL VALUE: NUMBER (%) OF PATIENTS (12-MONTH DATA): STUDY 212

Time Point Treatment Group	Normal- Borderline (≤ 6.19 mmol/L) [≤ 240 mg/dL]	High (> 6.19 mmol/L) [> 240 mg/dL]
Month 1		
RAPA + CsA (n= 73)	31 (42.5)[a]	42 (57.5)
RAPA (n = 70)	25 (35.7)	45 (64.3)
Month 3		
RAPA + CsA (n = 62)	25 (40.3)	37 (59.7)
RAPA (n = 62)	24 (38.7)	38 (61.3)
Month 6		
RAPA + CsA (n = 73)	27 (37.0)	46 (63.0)
RAPA (n = 74)	33 (44.6)	41 (55.4)
Month 12		
RAPA + CsA (n = 68)	40 (58.8)	28 (41.2)
RAPA (n = 67)	33 (49.3)	34 (50.7)

RAPA = Rapamune, CsA = cyclosporine.
a: All row mean score test p-values for RAPA + CsA vs RAPA were not significant (p > 0.05).

7.7.4.2 HDL Cholesterol

In both studies, the pattern of high-density lipoprotein (HDL) cholesterol levels paralleled that of total cholesterol. HDL cholesterol levels peaked between months 1 to 3 and then decreased. In general, HDL cholesterol levels were higher in the RAPA group.

Tables 7.7.4.2A and 7.7.4.2B show, for studies 310 and 212, respectively, the proportion of patients with low (< 0.9 mmol/L, or < 35 mg/dL), normal (0.9 to < 1.6 mmol/L, or 35 to < 62 mg/dL), and high (≥ 1.6 mmol/L, or ≥ 62 mg/dL) HDL cholesterol levels at various times after transplantation.

TABLE 7.7.4.2A. DISTRIBUTION OF PATIENTS BY FASTING HDL-CHOLESTEROL VALUE: NUMBER (%) OF PATIENTS (STUDY 310)

Time Point Treatment Group	Low (< 0.9 mmol/L) [<35 mg/dL]	Normal (0.9 to < 1.6 mmol/L) [35 to < 62 mg/dL]	High (≥ 1.6 mmol/L) [≥ 62 mg/dL]
Month 1			
RAPA + CsA (n = 146)	10 (6.9)[a]	63 (43.2)	73 (50.0)
RAPA (n = 152)	6 (4.0)	65 (42.8)	81 (53.3)
Month 3			
RAPA + CsA (n = 146)	5 (3.4)	78 (53.4)	63 (43.2)
RAPA (n = 150)	5 (3.3)	67 (44.7)	78 (52.0)
Month 6			
RAPA + CsA (n = 141)	8 (5.7)	82 (58.2)	51 (36.2)[a]
RAPA (n = 137)	4 (2.9)	68 (49.6)	65 (47.5)
Month 12			
RAPA + CsA (n = 144)	4 (2.8)	77 (53.5)	63 (43.8)
RAPA (n = 136)	10 (7.4)	57 (41.9)	69 (50.7)
Month 18			
RAPA + CsA (n = 85)	10 (11.8)	40 (47.1)	35 (41.2)
RAPA (n = 85)	6 (7.0)	35 (41.2)	44 (51.8)
Month 24			
RAPA + CsA (n = 18)	0	14 (77.8)	4 (22.2)[a]
RAPA (n = 19)	0	7 (36.8)	12 (63.2)

HDL = high density lipoprotein, RAPA = Rapamune, CsA = cyclosporine.
a: Mantel-Haenszel chi-square p-values for RAPA + CsA vs RAPA significant ($p < 0.05$).

TABLE 7.7.4.2B. DISTRIBUTION OF PATIENTS BY FASTING HDL-CHOLESTEROL VALUE: NUMBER (%) OF PATIENTS (STUDY 212)

Time Point Treatment Group	Low (< 0.9 mmol/L) [<35 mg/dL]	Normal (0.9 to < 1.6 mmol/L) [35 to < 62 mg/dL]	High (≥ 1.6 mmol/L) [≥ 62 mg/dL]
Month 1			
RAPA + CsA (n= 60)	2 (3.3)[a]	31 (51.7)	27 (45.0)
RAPA (n = 62)	4 (6.5)	35 (56.4)	23 (37.1)
Month 3			
RAPA + CsA (n= 57)	3 (5.3)	32 (56.1)	22 (38.6)
RAPA (n = 56)	4 (7.1)	27 (48.2)	25 (44.6)
Month 6			
RAPA + CsA (n= 65)	7 (10.8)	43 (66.1)	15 (23.1)
RAPA (n = 66)	2 (3.0)	39 (59.1)	25 (37.9)
Month 12			
RAPA + CsA (n= 60)	5 (8.3)	41 (68.3)	14 (23.3)
RAPA (n = 59)	5 (8.5)	36 (61.0)	18 (30.5)

HDL = high-density lipoprotein, RAPA = Rapamune, CsA = cyclosporine.
a: Row mean score test p-values for RAPA + CsA vs RAPA for months 1, 3, and 12 were not significant (p > 0.05), the p-value for month 6 is 0.023.

For both studies 310 and 212, the following points are noteworthy:

- At all time points, the majority of patients (> 89%) had normal or high HDL cholesterol levels.
- In general, elevated (≥ 1.6 mmol/L, or ≥ 62 mg/dL) HDL cholesterol levels occurred in a higher proportion of the RAPA group than of the RAPA + CsA group (51.8% vs 41.2%, respectively, at month 18 and 63.2% vs 22.2%, respectively, at month 24 for study 310 and 30.5% vs 23.3%, respectively, at month 12 for study 212).

7.7.4.3 LDL Cholesterol

In general, the mean low-density lipoprotein (LDL) cholesterol levels were similar in the 2 treatment groups for both studies (except the month 3 value in study 310, which was significantly higher for the RAPA group than for the RAPA + CsA group).

Tables 7.7.4.3A and 7.7.4.3B present the tabulations of LDL cholesterol values at intervals from months 1 to 24 in study 310 and months 1 to 12 in study 212 within 3 ranges: < 3.4 mmol/L (< 130 mg/dL), 3.4 to < 4.1 mmol/L (130 to < 160 mg/dL), and ≥ 4.1 mmol/L (≥ 160 mg/dL). In

both studies, the proportion of patients with elevated LDL cholesterol levels (≥ 4.1 mmol/L, or ≥ 160 mg/dL) was similar in the 2 treatment groups, and decreased from month 6 to month 18 in study 310. The percentage of patients with high LDL cholesterol (in both the RAPA + CsA and RAPA groups) ranged from approximately 18% to 39% in study 310 (months 12 to 24) and 26% to 28% in study 212 (month 12).

TABLE 7.7.4.3A. DISTRIBUTION OF PATIENTS BY RANGE OF FASTING LDL-CHOLESTEROL: NUMBER (%) OF PATIENTS (STUDY 310)

Time Point Treatment Group	Normal (< 3.4 mmol/L) [< 130 mg/dL]	Borderline (3.4 to <4.1 mmol/L) [130 to < 160 mg/dL]	High (≥ 4.1 mmol/L) [≥ 160 mg/dL]
Month 1			
RAPA + CsA (n = 132)	34 (25.8)[a]	41 (31.1)	57 (43.2)
RAPA (n = 141)	45 (31.9)	34 (24.1)	62 (44.0)
Month 3			
RAPA + CsA (n = 131)	48 (36.6)	25 (19.1)	58 (44.3)
RAPA (n = 128)	38 (29.7)	33 (25.8)	57 (44.5)
Month 6			
RAPA + CsA (n = 132)	57 (43.2)	32 (24.2)	43 (32.6)
RAPA (n = 125)	52 (41.6)	32 (25.6)	41 (32.8)
Month 12			
RAPA + CsA (n = 141)	68 (48.2)	34 (24.1)	39 (27.7)
RAPA (n = 121)	57 (47.1)	31 (25.6)	33 (27.3)
Month 18			
RAPA + CsA (n = 83)	43 (51.8)	25 (30.1)	15 (18.1)
RAPA (n = 80)	41 (51.2)	17 (21.3)	22 (27.5)
Month 24			
RAPA + CsA (n = 17)	8 (47.1)	3 (17.6)	6 (35.3)
RAPA (n = 18)	8 (44.4)	3 (16.7)	7 (38.9)

LDL = low density lipoprotein, RAPA = Rapamune, CsA = cyclosporine.
a: All Mantel-Haenszel chi-square p-values for RAPA + CsA vs RAPA were not significant (p > 0.05).

TABLE 7.7.4.3B. DISTRIBUTION OF PATIENTS BY RANGE OF FASTING LDL-CHOLESTEROL: NUMBER (%) OF PATIENTS (STUDY 212)

Time Point Treatment Group	Normal (< 3.4 mmol/L) [< 130 mg/dL]	Borderline (3.4 to <4.1 mmol/L) [130 to < 160 mg/dL]	High (≥ 4.1 mmol/L) [≥ 160 mg/dL]
Month 1			
RAPA + CsA (n = 56)	27 (48.2)[a]	13 (23.2)	16 (28.6)
RAPA (n = 50)	19 (38.0)	14 (28.0)	17 (34.0)
Month 3			
RAPA + CsA (n = 45)	23 (51.1)	9 (20.0)	13 (28.9)
RAPA (n = 45)	20 (44.4)	15 (33.3)	10 (22.2)
Month 6			
RAPA + CsA (n = 52)	18 (34.6)	14 (26.9)	20 (38.5)
RAPA (n = 54)	26 (48.2)	12 (22.2)	16 (29.6)
Month 12			
RAPA + CsA (n = 54)	29 (53.7)	10 (18.5)	15 (27.8)
RAPA (n = 50)	26 (52.0)	11 (22.0)	13 (26.0)

LDL = low density lipoprotein, RAPA = Rapamune, CsA = cyclosporine.
a: All row mean score test p-values for RAPA + CsA vs RAPA were not significant (p > 0.05).

7.7.4.4 Triglycerides

In both studies 310 and 212

- The triglyceride levels peaked at months 2 or 3 and decreased thereafter in both the RAPA + CsA and RAPA groups.

- Triglyceride levels in the RAPA group in general were numerically but not statistically, higher than those observed in the RAPA + CsA group except for month 1 in study 212 and for month 24 in study 310. The sirolimus concentrations were > 2-fold higher in the RAPA group.

The numbers of patients with elevated serum triglyceride levels were determined by applying the World Health Organization grades of severity.[29] Tables 7.7.4.4A and 7.7.4.4B show, for studies 310 and 212, respectively, the proportion of patients with normal to grade 1 (≤ 4.5 mmol/L, or ≤ 400 mg/dL), grade 2 (4.51 to 11.29 mmol/L, or 400 to 1000 mg/dL), or grade 3 (> 11.29 mmol/L, or > 1000 mg/dL) triglyceride levels at the corresponding time points. In both studies, the proportions of patients with grade 2 and 3 hypertriglyceridemia were similar in the RAPA + CsA and RAPA groups except at month 12 in study 310, where a higher proportion of

the RAPA group had grade 2 elevations. There were very few instances of grade 3 hypertriglyceridemia.

TABLE 7.7.4.4A. DISTRIBUTION OF PATIENTS BY FASTING TRIGLYCERIDE LEVEL: NUMBER (%) OF PATIENTS (STUDY 310)

Time Point Treatment Group	Normal-Grade 1 (≤ 4.5 mmol/L) [≤ 400 mg/dL]	Grade 2 (4.51-11.29 mmol/L) [400 to 1000 mg/dL]	Grade 3 (>11.29 mmol/L) [>1000 mg/dL]
Month 1			
RAPA + CsA (n = 171)	154 (90.1)	15 (8.8)	2 (1.2)
RAPA (n = 177)	163 (92.1)	14 (7.9)	0 (0.0)
Month 3			
RAPA + CsA (n = 162)	147 (90.7)	14 (8.6)	1 (0.6)
RAPA (n = 161)	140 (87.0)	21 (13.0)	0 (0.0)
Month 6			
RAPA + CsA (n = 153)	142 (92.8)	11 (7.2)	0 (0.0)
RAPA (n = 147)	135 (91.8)	11 (7.5)	1 (0.7)
Month 12			
RAPA + CsA (n = 156)	153 (98.1)	3 (1.9)	0 (0.0)
RAPA (n = 141)	128 (90.8)	13 (9.2)[a]	0 (0.0)
Month 18			
RAPA + CsA (n = 92)	89 (96.7)	3 (3.3)	0 (0.0)
RAPA (n = 91)	86 (94.5)	4 (4.4)	1 (1.1)
Month 24			
RAPA + CsA (n = 20)	18 (90.0)	2 (10.0)	0 (0.0)
RAPA (n = 20)	19 (95.0)	1 (5.0)	0 (0.0)

RAPA = Rapamune, CsA = cyclosporine.
a: Mantel-Haenszel chi-square p-values for RAPA + CsA vs RAPA significant (p = 0.005).

TABLE 7.7.4.4B. DISTRIBUTION OF PATIENTS BY FASTING TRIGLYCERIDE LEVEL: NUMBER (%) OF PATIENTS (STUDY 212)

Time Point Treatment Group	Normal-Grade 1 (≤ 4.5 mmol/L) [≤ 400 mg/dL]	Grade 2 (4.51-11.29 mmol/L) [400 to 1000 mg/dL]	Grade 3 (>11.29 mmol/L) [>1000 mg/dL]
Month 1			
RAPA + CsA (n= 70)	64 (91.4)[a]	6 (8.6)	0
RAPA (n = 70)	55 (78.6)	14 (20.0)	1 (1.4)
Month 3			
RAPA + CsA (n= 60)	47 (78.3)	12 (20.0)	1 (1.7)
RAPA (n = 61)	49 (80.3)	10 (16.4)	2 (3.3)
Month 6			
RAPA + CsA (n= 74)	59 (79.7)	15 (20.3)	0
RAPA (n = 71)	60 (84.5)	10 (14.1)	1 (1.4)
Month 12			
RAPA + CsA (n= 67)	60 (89.5)	7 (10.5)	0
RAPA (n = 64)	53 (82.8)	10 (15.6)	1 (1.6)

RAPA = Rapamune, CsA = cyclosporine.
a: Row mean score test p-values for RAPA + CsA vs RAPA for months 3, 6, and 12 were not significant ($p > 0.05$), the p-value for month 1 is 0.028.

In study 310, 4 patients in the RAPA + CsA group and 5 patients in the RAPA group discontinued treatment because of hyperlipemia (hypertriglyceridemia) by the data cutoff date of 03 Jan 2001. Only 1 patient in study 212 (RAPA group) discontinued because of hyperlipemia (hypertriglyceridemia).

7.7.4.5 Overall Discussion of Serum Lipids for Patients in Studies 310 and 212

The results from studies 310 and 212 were consistent with regard to lipid values.

- Cholesterol and triglyceride levels in both treatment groups peaked at months 2 or 3 and decreased thereafter.
- Similar cholesterol levels were noted in the RAPA + CsA and RAPA groups, despite significantly higher concentrations of sirolimus in the RAPA group.
- In general, triglyceride levels were numerically, but not statistically, higher in the RAPA group.
- Most patients had normal or elevated HDL cholesterol levels.

- Similar LDL cholesterol levels and a similar proportion of patients with elevated LDL cholesterol levels were noted in the 2 treatment groups.

7.7.5 Other Biochemistry Data

Elevations of cytosolic enzymes (lactate dehydrogenase [LDH] and serum aminotransferases) have been observed sporadically in Rapamune-treated patients. The origin of these transient abnormalities is often not apparent. These abnormalities have not been accompanied by signs or symptoms of clinical disease of muscle, heart, lung, or liver or accompanied by other localizing enzyme abnormalities, such as alkaline phosphatase (liver).

7.7.5.1 Alanine Aminotransferase and Aspartate Aminotransferase

In both studies 310 and 212, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels were generally higher in the RAPA group. The elevations were generally mild. Very few patients had clinically important elevations of liver enzymes.

Table 7.7.5.1A (study 310) shows that the number of patients with reported AST or ALT values greater than 5 times (AST: ≥200 IU/L; ALT ≥ 275 IU/L) or 10 times (AST: ≥ 400 IU/L; ALT ≥ 550 IU/L) the normal values were few and were similar in the 2 groups. Further, as shown in Table 7.7.5.1B, many of these patients had evidence of viral hepatitis, which may have contributed to the elevations in the aminotransferase values.

TABLE 7.7.5.1A. NUMBER (%) OF PATIENTS WITH SERUM AMINOTRANSFERASE VALUES 5 OR 10 TIMES GREATER THAN THE NORMAL (CUMULATIVE DATA): STUDY 310

Serum Aminotransferase Value	RAPA + CsA (n = 215)	RAPA (n = 215)
AST		
≥ 200 IU/L	6 (2.8)	3 (1.4)
≥ 400 IU/L	3 (1.4)	0 (0.0)
ALT		
≥ 275 IU/L	6 (2.8)	6 (2.8)
≥ 550 IU/L	4 (1.9)	1 (0.5)

RAPA = Rapamune, CsA = cyclosporine, AST = aspartate aminotransferase (SGOT), ALT = alanine aminotransferase (SGPT).

TABLE 7.7.5.1B. RANDOMLY ASSIGNED PATIENTS WHO REPORTED AT LEAST 1 ALT VALUE GREATER THAN 5 TIMES THE UPPER LIMIT OF NORMAL (ALT ≥ 275 IU/L) – (CUMULATIVE DATA): STUDY 310

Therapy Group Patient No.	Time Slot, Month	Value (IU/L)	Cause of Elevated Liver Enzymes
RAPA + CsA Group			
310-3505	4	670[a]	Hepatitis B
310-3814	4 to 7	347-804[a]	Hepatitis B reactivation
310-5807	3	301	No specific reason
310-6110	3 to 5, 7	323-770[a]	Increased liver enzymes since study day 7
310-6912	5	555[a]	Hepatitis B core antigen positive
310-7202	8	332	No specific reason
RAPA Group			
310-3821	5	297	Hepatitis B
310-4102	5	377	No specific reason
310-8506	4	460	CMV hepatitis
310-8512	12	539-680[a]	Hepatitis (no serology, drug-induced)
310-8708	4	297-322	Hepatitis (no serology, drug-induced)
310-5203	15	313	Suspected viral infection or sirolimus toxicity

RAPA = Rapamune, CsA = cyclosporine, ALT = alanine aminotransferase (SGPT), CMV = cytomegalovirus.
a: Values greater than 10 times the normal values (ALT ≥ 550 IU/L).

Figures 7.7.5.1A and 7.7.5.1B show box and whisker plots for AST and ALT values, respectively, for the RAPA + CsA and RAPA groups at months 6 and 12 (study 212). In study 212, the aminotransferase elevations were generally mild. At month 12, only 1 AST reading was > 150 (IU/L) and 1 ALT reading > 150 (IU/L).

FIGURE 7.7.5.1A. BOX AND WHISKER PLOT OF AST
AT MONTHS 6 AND 12 FOR GROUPS RAPA + CsA AND RAPA - STUDY 212

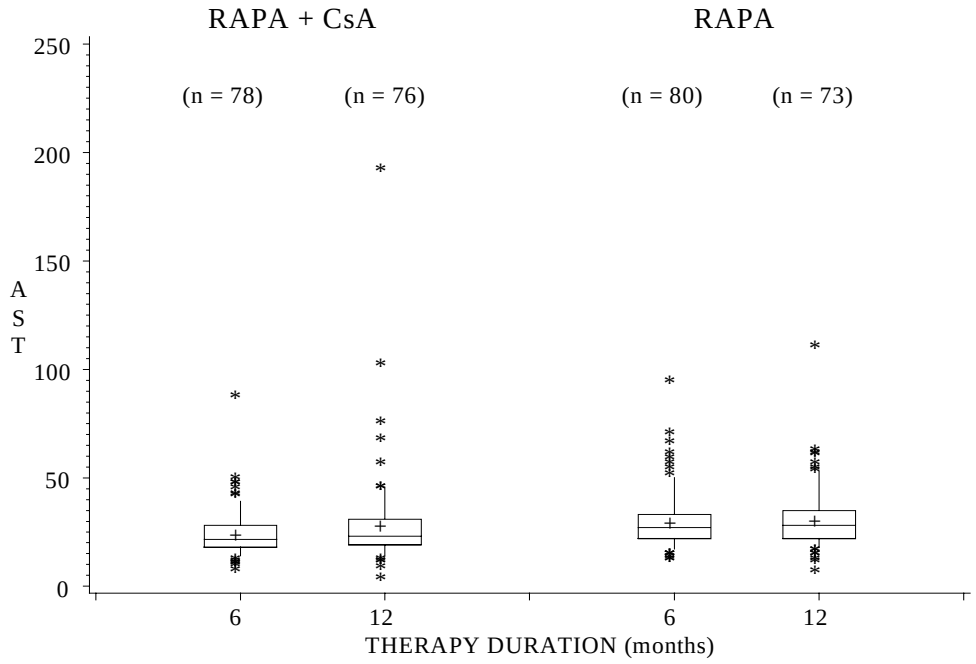
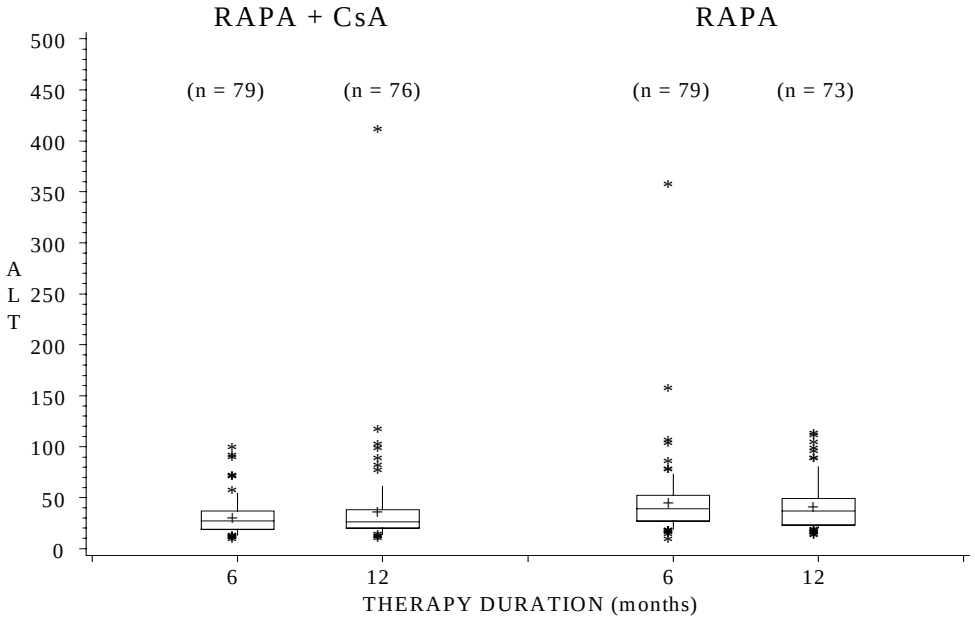


FIGURE 7.7.5.1B. BOX AND WHISKER PLOT OF ALT
AT MONTHS 6 AND 12 FOR GROUPS RAPA + CsA AND RAPA - STUDY 212



7.7.5.2 Lactate Dehydrogenase

Generally, higher lactate dehydrogenase (LDH) values were noted in the RAPA group. The differences of the comparisons reached statistical significance in study 310 at months 6, 9, 12, and 15. The clinical importance of these findings is uncertain.

7.7.5.3 Alkaline Phosphatase

In both studies, the alkaline phosphatase values were similar in the 2 treatment groups over time.

7.7.5.4 Overall Summary of Other Biochemistry Values for Studies 310 and 212

The results from both studies showed generally higher ALT/AST and LDH levels in the RAPA group. The elevations of ALT/AST and LDH concentrations in the RAPA group were generally mild, with very few patients showing clinically important elevations of these liver enzymes. Many of the patients (study 310) who had ALT/AST values ≥ 5 to 10 times the upper limits of normal had evidence of viral hepatitis. The mean levels of alkaline phosphatase were similar over time in the 2 treatment groups in both studies.

7.8 Vital Signs and Weight

7.8.1 Mean Changes in Body Weight

Results for body weight were similar in studies 310 and 212.

- Patients in both treatment groups gained weight over time.
- There were no significant differences in weight between the RAPA + CsA and RAPA groups, with the exception of the isolated higher mean weight in the RAPA + CsA group at month 6 for study 310 and at month 1 for study 212.

7.8.2 Mean Changes in Blood Pressure

In study 310, after randomization, both the systolic and diastolic blood pressures were significantly lower in the RAPA group from months 6 to 24 than in the RAPA + CsA group.

In study 212, the mean systolic blood pressure was generally lower in the RAPA group, but the comparison with the RAPA + CsA group reached statistical significance only at month 12. The diastolic blood pressure values were similar in the RAPA + CsA and RAPA groups.

7.8.3 Mean Changes in Heart Rate

In study 310, patients in the RAPA group had a significantly faster mean heart rate than did patients in the RAPA + CsA group at months 6, 9, 12, 15, and 18. In study 212, heart rate was similar for the 2 treatment groups at all time points.

7.8.4 Overall Summary of Vital Signs and Weight for Studies 310 and 212

The most important safety finding regarding vital signs was the observation of significantly lower systolic and diastolic blood pressures (study 310) in patients in the CsA-elimination arm (RAPA group). The attendant long-term cardiovascular benefits of maintaining normal blood pressure are well known.

7.9 Safety Conclusions From Studies 310 and 212

A comprehensive safety analysis is presented for patients in the prerandomization phase (study 310) and the postrandomization phase (studies 310 and 212). In trial 310, 525 and 430 patients were evaluated for safety in the prerandomization and postrandomization phases, respectively. A total of 246 patients were enrolled in study 212, and the results for 245 patients who received at least 1 dose of study drug are included in this summary. Of these, 197 were randomly assigned into 1 of 2 treatment groups, and 49 patients were enrolled in the nonrandomized group. Data summarized represent either final 12-month data (study 212) or cumulative data (up to the cutoff date of 03 Jan 2001 for study 310).

The results from the 2 studies were consistent. The data demonstrated that immunotherapy with concentration-controlled sirolimus with CsA elimination has an acceptable safety profile and is associated with several distinct advantages related to the withdrawal of CsA.

The safety evaluation of the patients in the prerandomization phase of study 310 showed the following:

- The most common TEAEs were hyperlipemia (hypertriglyceridemia), peripheral edema, hypercholesteremia, hypertension, local reaction to procedure, diarrhea, creatinine increased, and anemia. These events were similar to those observed in previous Rapamune phase 3 studies in which Rapamune was combined with full-dose CsA.

- Ninety-five (95, 18%) patients either discontinued the treatment before randomization or were not eligible for randomization. As is true for other immunosuppressive regimens, the

most common causes of discontinuation during the prerandomization period were adverse events (74%) and unsatisfactory response (13%). The most frequent adverse events leading to discontinuation were abnormal kidney function or kidney tubular necrosis (9 cases), local reaction to procedure (7 cases), and thrombotic thrombocytopenic purpura (8 cases).

In the postrandomization evaluation for the 2 studies, the regimen of concentration-controlled sirolimus with CsA elimination (the RAPA group) compared with therapy with fixed-dose Rapamune and standard-dose CsA (the RAPA + CsA group) was associated with the following:

- Significantly better renal function, which persisted through month 12 (in study 212) and month 24 (in study 310). In both studies, calculated GFR values were significantly higher at months 6, 9, and 12 in the RAPA group, and up to month 24 for study 310.

- Significantly lower serum urea (study 310) and BUN (study 212) levels, which are likely reflective of better GFR values associated with CsA elimination.

- Higher mean magnesium levels, lower mean potassium levels, and lower mean uric acid levels—all of which may be reflective of less CsA exposure and greater sirolimus exposure in the RAPA group.

- Significantly lower systolic and diastolic blood pressures from months 6 to 24 (study 310).

- Significantly lower incidence of CsA-related adverse events including 1) hypertension and edema (studies 310 and 212), 2) hypomagnesemia, hypervolemia, and dyspnea (study 212), and 3) CsA toxicity, hyperuricemia, and creatinine increased (study 310).

- Thrombocytopenia, hypokalemia, and liver function test abnormalities were more commonly reported in the RAPA group in both studies, and were possibly related to the greater Rapamune exposure in these patients. Increased ALT was reported more frequently in the RAPA group in study 310. Diarrhea and atrial fibrillation were reported more frequently in the RAPA group in study 212.

Other safety observations (postrandomization) for the RAPA + CsA and RAPA groups in both studies include the following:

- The rate of discontinuation at 1 year was similar in the 2 treatment groups in study 212 (21% and 25%, the RAPA + CsA and RAPA groups, respectively) and in study 310 (27% and 30%, the RAPA + CsA and RAPA groups, respectively; cumulative data).

- The rates and types of infections were similar in the 2 treatment groups.

- Similar cholesterol levels were noted in the 2 treatment groups, despite significantly higher concentrations of sirolimus in the RAPA group.

- Triglyceride levels were generally higher in the RAPA group.

- It is noteworthy that by month 12 the mean cholesterol and triglyceride levels were similar to those observed in the control arms of studies 301 and 302. These patients (control arms of 301 and 302) who received baseline immunotherapy with CsA and steroids were never treated with Rapamune. Many of the Rapamune-treated patients did require therapy with statins and/or fibrates.

- Seventy-three percent (73%) of the patients in both the RAPA + CsA and the RAPA groups in study 310 required treatment with statins while receiving treatment. Similarly, 24% and 25% of the patients in the RAPA + CsA and the RAPA groups, respectively, in study 310 were treated with fibrates (cumulative data). During the course of the first year of treatment in study 212, statins were required by 57% and 65% of the patients in the RAPA + CsA and the RAPA groups, respectively, while fibrates were used to treat 11% and 8% of the patients in the RAPA + CsA and the RAPA groups, respectively.

- A safety evaluation of approximately 1000 patients (from studies 301, 302, 212, and 310) treated with statins showed that these agents are well tolerated when administered concomitantly with Rapamune.

- The great majority of patients had normal or elevated HDL cholesterol levels. At month 12, 31% to 51% of the RAPA group had elevated HDL cholesterol levels ≥ 1.6 mmol/L (≥ 62 mg/dL).

- LDL cholesterol levels were similar in the 2 treatment groups. At month 12, 26% to 28% of the patients had elevated levels of LDL cholesterol (≥ 4.1 mmol/L, or ≥ 400 mg/dL).

- Hematologic parameters were similar in the 2 groups, with the exception of significantly lower mean platelet counts in the RAPA group in study 310. The mean platelet counts in both treatment groups for studies 212 and 310 were generally well within the normal range.

- The results from both studies showed generally higher ALT/AST and LDH levels in the RAPA group. These elevations were generally mild, and very few patients had clinically important elevations of these liver enzymes. Many patients (study 310) who had ALT/AST values ≥ 5 to 10 times the upper limits of normal had evidence of viral hepatitis. The mean levels of alkaline phosphatase were similar over time in the 2 treatment groups for both studies.

- Patient and graft survival were excellent in both treatment groups. Cardiovascular events and infection were the main causes of death. ATN, vascular events (including HUS), and acute rejection were the main causes of (pure) graft loss.

- The overall rate of malignancy was low: 1.6% (12-month) and 5.1% (cumulative data) in studies 212 and 310, respectively. There were 4 cases of lymphoma/PTLD/leukemia in study 310. There was 1 case of PTLD in study 212; however, the diagnosis of PTLD was never confirmed, and the patient remained in and completed the study.

8 CLINICAL PHARMACOKINETICS

8.1 A Review of the Pharmacokinetic Characteristics of Sirolimus

Detailed descriptions of the pharmacokinetic characteristics of sirolimus were included in the previous NDA submissions for Rapamune Oral Solution (NDA 21-083) and Rapamune Tablets (NDA 21-110).

Table 8.1A presents a summary of the absorption, distribution, and elimination characteristics of sirolimus after administration of oral solution, based on (a) a 2-stage population analysis of data from renal transplant patients during phases 1, 2, and 3[30] and (b) data from individual studies in healthy subjects and renal transplant patients during phase 1. The results from an in vitro protein binding study are also included.

TABLE 8.1A. SIROLIMUS PHARMACOKINETIC CHARACTERISTICS BASED ON DATA AFTER ADMINISTRATION OF RAPAMUNE ORAL SOLUTION

Characteristic	Comment
Absorption	• Rapid absorption (median t_{max} ~ 1.0 hours in renal allograft patients after multiple oral doses).[a] • Low systemic availability (F ~ 14% in stable renal transplant patients).[31] • Dose proportional (1 to 12 mg/m^2 in stable renal transplant patients).[32,33]
Distribution	• Extensively bound to plasma proteins (~ 92%).[34] • Extensive partitioning into formed blood elements (mean B/P ratio = 36 in stable and posttransplant renal allograft patients). • Large steady-state volume of distribution (~ 1.6 L/kg in stable renal transplant patients).
Elimination	• Metabolized to 7 major inactive metabolites.[35] • Low urinary excretion (2.2% in healthy subjects).[36] • Biphasic/triphasic elimination characteristics. • Prolonged terminal half-life ($t_{1/2}$ ~ 62 hours after multiple-dose administration in stable renal transplant patients). • Highly variable steady-state, oral-dose clearance (intersubject CV% ~ 50% and intrasubject CV% ~ 26% among stable and posttransplant renal allograft patients).

F = systemic availability, B/P = blood/plasma, CV% = percent coefficient of variation.
a: Studies 112 (n = 27), 203 (n = 27), and 301 (n = 34).

Sirolimus is known to be a substrate for the intestinal[37] and hepatic[38] cytochrome P450 isozyme CYP3A4. Sirolimus metabolism occurs by O-demethylation and/or hydroxylation; 7 major metabolites, which include hydroxy, demethyl, and hydroxydemethyl analogs, are identifiable in whole blood.[35] 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. The

demethyl and hydroxy metabolites combined show ≤ 30% of the in vitro immunosuppressive activity of sirolimus. Sirolimus is also a substrate for P-glycoprotein (a multidrug efflux pump).[37,39]

Table 8.1B presents a comparative summary of the absorption, distribution, and elimination characteristics of sirolimus after administration of oral solution and tablets (oval). The results are based on a (a) a 2-stage population analysis of data from renal transplant patients during phases 1, 2, and 3[40] and (b) data from individual studies in healthy subjects during phase 1.

TABLE 8.1B. COMPARATIVE SIROLIMUS PHARMACOKINETIC CHARACTERISTICS AFTER ADMINISTRATION OF RAPAMUNE TABLETS (OVAL) OR RAPAMUNE ORAL SOLUTION

Characteristic	Population	Comment
Absorption	HS	• Rapamune tablet (5 mg) was dose proportional over a 5 to 40 mg dose range.[41] • The systemic availability of sirolimus from Rapamune tablets is approximately 17% (ie, 27% greater than Rapamune oral solution).
	RA	• Less rapid absorption from Rapamune tablet (median t_{max} = 3.0 hours) than from Rapamune oral solution (median t_{max} = 1.5 hours) after multiple-dose administration.[a,b] • Dose-normalized C_{max} was not significantly different after multiple-dose administrations of Rapamune tablet or Rapamune oral solution.
Distribution	HS	• Oral-dose Vss/F (weight adjusted) was not significantly different after single-dose administrations of Rapamune tablet or Rapamune oral solution.
Elimination	HS	• Terminal elimination half-life ($t_{1/2}$) and oral-dose CL/F (weight adjusted) were not significantly different after single-dose administrations of Rapamune tablet or Rapamune oral solution.
	RA	• Oral-dose CL/F (weight adjusted) was not significantly different after multiple dose administrations of Rapamune tablet or Rapamune oral solution.

HS = healthy subjects; RA = renal allograft patients, Vss/F = apparent oral-dose steady-state volume of distribution, CL/F = apparent oral-dose clearance.
a: Tablet: studies 306 (n = 19) and 309 (n= 13).
b: Solution: studies 112 (n= 27), 203 (n = 13), 301(n = 18), and 309 (n = 17).

8.1.1 Impact of Pharmacokinetic Characteristics on Concentration-Controlled Drug Administration

The data from individual studies after the administration of Rapamune oral solution also permitted the assessment of 5 sirolimus pharmacokinetic characteristics that are essential to concentration-controlled dose administration: (1) dose proportionality, (2) the relationship between trough vs area under the concentration-time curve (AUC) during the dose-interval at

steady-state, (3) the time to reach steady-state (4) the loading dose, and (5) the maximum daily dose.

As shown in Tables 8.1A and 8.1B , the dose-proportionality of sirolimus extends over a range of 1 mg/m^2/day (ie, approximately 2 mg/day) to 40 mg/day. This range is sufficient to cover any dose adjustments that would be required during concentration-controlled dose administration of sirolimus.

The relationship between sirolimus whole blood troughs and AUCs over a 24-hour steady-state dose interval was determined in study 301, a pivotal trial conducted with renal allograft patients who received daily oral doses of sirolimus (oral solution) during coadministration with CsA.[33] Sirolimus pharmacokinetic data were collected at selected clinical sites at months 1, 3, and 6 after transplant in 42 patients receiving sirolimus doses of either 2 or 5 mg/day. Based on linear regression analysis, the relationship between troughs and AUC was expressed as $C_{min,24h} = -0.081 + 0.0294 \bullet AUC_{0-24h}$, ($R^2 = 0.96$). There was an excellent relationship between troughs and AUC as shown by the value of R^2 (explained variance), which indicates that troughs may be used as a surrogate for AUC during dose adjustments.

The time to reach steady-state and the loading dose were assessed by using data from study 112. Study 112 was an early phase 1 trial that was conducted to determine safety and pharmacokinetics in stable renal allograft patients after multiple twice a day (BID) oral doses of Rapamune oral solution during coadministration with CsA.[42] Based on a review of the whole blood sirolimus trough concentrations over days 1 to 14, it was determined that mean steady-state trough concentrations were reached within 5 to 7 days after the start of dose administration. However, the time to steady state was as long as 13 days in individual patients. These data suggest that a blood sample for the determination of a steady-state trough should not be drawn for at least at least 5 to 7 days after the previous dose adjustment. The mean ± standard deviation (SD; range) and median sirolimus loading dose required to rapidly achieve steady-state, expressed as the dose ratio (loading dose/maintenance dose), was 2.56 ± 0.70 (range, 1.37 to 4.02, n = 26) and 2.54, respectively. For convenience, a sirolimus oral loading dose of approximately 3 times the maintenance dose may be administered to patients when individual loading-dose estimates cannot be made.

The maximum daily dose of sirolimus can be assessed based on the results from study 111, an early phase 1 trial that was conducted to determine safety and pharmacokinetics in stable renal allograft patients after single oral doses of Rapamune oral solution during coadministration with

CsA.[43] Six (6) sirolimus doses ranging from 3 to 34 mg/m^2 were assessed in groups of 3 patients each. The mean ± SD dose of sirolimus tested in the highest dose group was 60.8 ± 6.8 mg (n = 3). Nevertheless, a more conservative maximum dose of 40 mg on any day was recommended in pivotal trial 310 for purposes of rapidly achieving concentrations within the 20 to 30 ng/mL target range.

8.1.2 Factors Affecting the Pharmacokinetics of Sirolimus

Pharmacokinetic studies were conducted to specifically assess (a) effects of food and of the liquid used for administration, (b) pharmacokinetics in special populations, and (c) potential drug interactions. Each of these types of studies is briefly discussed below.

8.1.2.1 Effects of Food and Liquid Used for Administration

8.1.2.1.1 Food Effect

In 22 healthy subjects receiving sirolimus oral solution, a high-fat breakfast (1.88 kcal, 54.7% fat) altered the bioavailability characteristics of sirolimus.[44] Compared with fasting, a 34% decrease in the peak blood sirolimus concentration (C_{max}), a 3.5-fold increase in the time-to-peak concentration (t_{max}), and a 35% increase in AUC was observed. After administration of sirolimus tablets and a high-fat meal in 24 healthy subjects, C_{max}, t_{max}, and AUC showed increases of 65%, 32%, and 23%, respectively.[45] Thus, a high-fat meal produced differences in the effects of the 2 formulations with respect to rate of absorption, but not extent of absorption. To minimize variability, both sirolimus oral solution and tablets should be taken consistently with or without food.

8.1.2.1.2 Liquid Used for Administration

Bioequivalence testing based on AUC and C_{max} showed that sirolimus administration with orange juice is equivalent to administration with water.[46] Therefore, orange juice and water may be used interchangeably as administration liquids for sirolimus oral solution. Grapefruit juice reduces CYP3A4-mediated metabolism of sirolimus and must not be used for dilution.[47]

8.1.2.2 Special Populations

8.1.2.2.1 Pediatric Patients

Limited pharmacokinetic data are available for pediatric patients. Table 8.1.2.2.1A summarizes pharmacokinetic data obtained with pediatric dialysis patients with chronically impaired renal function.[48]

TABLE 8.1.2.2.1A. SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS WITH STABLE CHRONIC RENAL FAILURE MAINTAINED WITH HEMODIALYSIS OR PERITONEAL DIALYSIS: (1, 3, 9, 15 mg/m^2 SINGLE DOSE OF SIROLIMUS)

Age Group (y)	n	t_{max} (h)	$t_{1/2}$ (h)	CL/F (mL/h/kg)
5-11	9	1.1 ± 0.5	71 ± 40	580 ± 450
12-18	11	0.79 ± 0.17	55 ± 18[a]	450 ± 230[a]

SD = standard deviation, CL/F = apparent oral-dose clearance (weight adjusted).
a: Mean values based on n = 9.

8.1.2.2.2 Sex

After the administration of sirolimus oral solution, sirolimus oral dose clearance in men was 12% lower than in women; male subjects had a significantly longer $t_{1/2}$ than female subjects (72.3 hours versus 61.3 hours).[30] The effects of sex observed after administration of sirolimus tablets were similar to those observed after administration of sirolimus oral solution.[40] These pharmacokinetic differences do not require dose adjustment based on sex.

8.1.2.2.3 Race

Large phase 3 trials were conducted with sirolimus oral solution and CsA oral solution MODIFIED (eg, Neoral oral solution) and cyclosporine capsules MODIFIED (eg, Neoral soft gelatin capsules). The results showed there were no significant differences in mean trough sirolimus concentrations over time between black (n = 139) and nonblack (n = 724) patients during the first 6 months after transplantation at sirolimus doses of 2 mg/day and 5 mg/day.[33,49] Similarly, after administration of sirolimus tablets (2 mg/day) in a phase 3 trial, mean sirolimus concentrations over 6 months were not significantly different among black (n = 51) and nonblack (n = 128) patients.[50]

8.1.2.2.4 Hepatic Impairment

Sirolimus (15 mg) was administered as a single oral dose to 18 subjects with normal hepatic function and to 18 patients with hepatic impairment of Child-Pugh classification A or B, in

which hepatic impairment was primary and not related to an underlying systemic disease.[51] The mean ± SD pharmacokinetic parameters following the administration of sirolimus oral solution are shown in Table 8.1.2.2.4A.

TABLE 8.1.2.2.4A. SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN 18 HEALTHY SUBJECTS AND 18 PATIENTS WITH HEPATIC IMPAIRMENT (15-mg SINGLE DOSE)

Population	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng•h/mL)	CL/F (mL/h/kg)
Healthy subjects	78.2 ± 18.3	0.83 ± 0.17	970 ± 272	215 ± 76
Subjects with hepatic impairment	77.9 ± 23.1	0.84 ± 0.17	1567 ± 616	144 ± 62

SD = standard deviation, $AUC_{0-\infty}$ = total are under the concentration curve after a single dose, CL/F = apparent oral-dose clearance (weight adjusted).

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

8.1.2.2.5 Renal Impairment

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

8.1.2.2.6 Geriatric Patients

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

8.1.2.3 Drug Interactions

As indicated in section 8.1A, sirolimus is extensively metabolized by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp), located in the small intestine. Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by substances that affect these proteins.

Table 8.1.2.3A summarizes the effect of coadministered drugs on the pharmacokinetics of sirolimus based on the administration of sirolimus oral solution.

TABLE 8.1.2.3A. RATIOS OF SIROLIMUS PHARMACOKINETIC PARAMETERS AFTER COADMINISTRATION OF RAPAMUNE ORAL SOLUTION WITH POTENTIALLY INTERACTING DRUGS

		Ratio of Sirolimus Pharmacokinetic Parameters[a,b]				
Population	Interacting Drug	t_{max}	C_{max}	$t_{1/2}$	AUC	CL/F
Healthy subjects	Acyclovir	0.95	↔	↔	↔	↔
	Atorvastatin	-	-	↔	↔	↔
	Cyclosporine microemulsion capsules (simultaneous dose administration)	1.92	2.16	↔	3.30	0.30
	Cyclosporine microemulsion capsules (CsA 4 h before SRL)	1.58	1.37	1.10	1.80	0.56
	Digoxin	1.03	↔	↔	↔	↔
	Diltiazem	1.29	1.43	0.85	1.60	0.38
	Glyburide	↔	↔	↔	↔	↔
	Ketoconazole	1.38	4.42	↔	10.9	0.085
	Nifedipine	↔	↔	↔	↔	↔
	Norgestrel/ethinyl estradiol	-	-	0.86	1.08	↔
	Rifampin	↔	0.29	↔	0.18	5.53
	Tacrolimus	1.08	↔	↔	↔	↔
Renal transplant	Sulfamethoxazole/trimethoprim	↔	↔	-	↔	-
	Prednisolone	-	-	-	↔	-
Psoriasis	Cyclosporine oral solution (simultaneous dose administration)	-	-	-	1.75[c]	-

CL/F = apparent oral-dose clearance, SRL = sirolimus.
a: Ratio = (sirolimus + drug): (sirolimus alone).
b: ↔ = no statistically significant change.
c: Ratio of average sirolimus trough concentrations.

Brief summaries of the results of clinically important drug-interaction studies are provided below, together with dose recommendations for combined use of sirolimus with the listed agents.

Cyclosporine Capsules MODIFIED (Neoral Soft Gelatin Capsules) with Rapamune Oral Solution: In a single-dose drug-drug interaction study, 24 healthy subjects were administered

10 mg of sirolimus either simultaneously or 4 hours after a 300-mg dose of Neoral soft gelatin capsules.[52] With simultaneous administration, the mean C_{max} and AUC of sirolimus were increased by 116% and 230%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after administration of Neoral soft gelatin capsules, sirolimus C_{max} and AUC were increased by 37% and 80%, respectively, compared with administration of sirolimus alone.

Mean C_{max} and AUC for CsA were not significantly affected when sirolimus was given simultaneously or when administered 4 hours after Neoral soft gelatin capsules. However, after multiple-dose administration of sirolimus given 4 hours after Neoral in renal transplant patients over a period of 6 months, CsA oral-dose clearance was reduced, and lower doses of Neoral soft gelatin capsules were needed to maintain target CsA concentration.[33]

Cyclosporine Capsules MODIFIED (Neoral Soft Gelatin Capsules) with Rapamune Tablets: In a single-dose drug-drug interaction study, 24 healthy subjects were administered 10 mg of sirolimus (Rapamune tablets) either simultaneously or 4 hours after a 300-mg dose of Neoral soft gelatin capsules.[53] With simultaneous administration, mean C_{max} and AUC were increased by 6.1-fold and 2.5-fold, respectively, relative to administration of sirolimus alone. However, when given 4 hours after CsA administration, sirolimus C_{max} and AUC were both increased by only 33% compared with administration of sirolimus alone.

In a large, randomized, multicenter, controlled trial in renal transplant recipients, there was no significant difference in C_{max} and AUC for either sirolimus tablets or oral solution for when sirolimus was administered 4 hours after CsA.[50]

Because of the effect of Neoral soft gelatin capsules on sirolimus pharmacokinetics, it is recommended that sirolimus should be taken 4 hours after administration of Neoral oral solution and Neoral soft gelatin capsules.

Cyclosporine Oral Solution (Sandimmune Oral Solution): In a multiple-dose study in 150 patients with psoriasis, sirolimus 0.5, 1.5, and 3 mg/m^2/day was administered simultaneously with Sandimmune oral solution (CsA oral solution) 1.25 mg/kg/day.[54] The increase in average sirolimus trough concentrations ranged from 67% to 86% relative to when sirolimus was administered with CsA. The intersubject variability (%CV) for sirolimus trough concentrations ranged from 39.7% to 68.7%. There was no significant effect of multiple-dose sirolimus on CsA

trough concentrations following Sandimmune oral solution (CsA oral solution) administration. However, the %CV was higher (range, 85.9% to 165%) than those from previous studies.

Sandimmune oral solution is not bioequivalent to Neoral oral solution, and should not be used interchangeably. Although there are no published data comparing Sandimmune oral solution with SangCya oral solution, they should not be used interchangeably. Likewise, Sandimmune soft gelatin capsules are not bioequivalent to Neoral soft gelatin capsules and should not be used interchangeably.

Diltiazem: The simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy subjects significantly affected the bioavailability of sirolimus.[55] Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem. If diltiazem is administered, sirolimus should be monitored and a dose adjustment may be necessary.

Ketoconazole: Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 1.4-fold, and 10.9-fold, respectively.[56] However, the terminal $t_{1/2}$ of sirolimus was not changed. It is recommended that sirolimus should not be coadministered with ketoconazole. However, if it is the opinion that the benefit outweighs the risk due to the interaction, monitoring of whole blood sirolimus concentrations and sirolimus dose reduction must be considered.

Rifampin: Pretreatment with multiple doses of rifampin, 600 mg daily for 14 days, greatly decreased sirolimus exposure after a single 10-mg dose of oral solution in 16 healthy subjects.[57] Rifampicin increased the clearance of sirolimus by approximately 5.5-fold and decreased AUC and C_{max} by approximately 82% and 71%, respectively. In patients in whom rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered. However, if it is the opinion that the benefit outweighs the risk due to the interaction, monitoring of whole blood sirolimus concentrations and sirolimus dose increase must be considered.

Other drug interactions: Inhibitors of CYP3A4 may decrease the metabolism of sirolimus and increase sirolimus blood levels (eg, calcium channel blockers: nicardipine, verapamil; antifungal agents: clotrimazole, fluconazole, itraconazole; macrolide antibiotics: clarithromycin,

erythromycin, troleandomycin; gastrointestinal prokinetic agents: cisapride, metoclopramide; other substances: bromocriptine, cimetidine, danazol, protease inhibitors). Inducers of CYP3A4 may increase the metabolism of sirolimus and decrease sirolimus blood levels (eg, anticonvulsants: carbamazepine, phenobarbital, phenytoin; antibiotics: rifabutin). Inhibitors of P-gp may decrease the efflux of sirolimus from intestinal cells and increase sirolimus levels.

Grapefruit juice affects CYP3A4-mediated metabolism and should therefore be avoided.[47]

Drugs that may be coadministered without dose adjustment: No clinically important interaction was observed between sirolimus and any of the following substances: acyclovir, atorvastatin, digoxin, glyburide (glibenclamide), methylprednisolone, nifedipine, norgestrel/ethinyl estradiol, prednisolone, tacrolimus, and trimethoprim/sulfamethoxazole.

8.2 Overview of Concentration-Controlled Studies

Sirolimus concentration-time data were obtained after administration of Rapamune oral solution and tablets to renal allograft recipients in 6 clinical studies. Trough sirolimus concentration profiles were determined (1) to characterize the pharmacokinetic (PK) behavior of sirolimus during concomitant administration with CsA and corticosteroids and after withdrawal of CsA from the regimen and (2) to determine the therapeutic window of sirolimus during a maintenance regimen after withdrawal of CsA.

The data from individual studies were summarized by using noncompartmental PK methods. In addition, a formal concentration-effect analysis was conducted for 1 pivotal phase 3 study in renal transplant recipients during concomitant administration of Rapamune tablets, CsA, and corticosteroids.

The clinical studies are listed by study type, time period, formulation, and analyte in Table 8.2A.

TABLE 8.2A. PHARMACOKINETIC DATA COLLECTED AMONG CONCENTRATION-CONTROL STUDIES IN RENAL ALLOGRAFT RECIPIENTS

Study Type	Time Period	RAPA Formulation	Study Number	------Analyte------ RAPA	CsA
Pivotal study 310	≤ 1 year after transplant	Tablets	0468E1-310-GL	X	X
Supportive study 212	≤ 1 year after transplant	Oral solution	0468E1-212-GL	X	X
Supportive RAPA vs CsA	≤ 1 year after transplant	Oral solution	0468E1-207-EU	X	-
		Oral solution	0468E1-210-EU	X	-
Supportive long-term	> 1 year after transplant	Oral solution	0468E1-207-EU	X	-
		Oral solution	0468E1-210-EU	X	-
		Tablets	0468E1-310-GL	X	X
		Solution and tablets	0468E1-306-GL	X	X
		Solution and tablets	0468E1-311-GL	X	X

Abbreviations: RAPA = Rapamune, CsA = Cyclosporine.

Among the studies in Table 8.2A, 4 clinical studies (310, 212, 207, 210) were conducted by using concentration-control of whole blood sirolimus trough concentrations. In 2 studies (310, 212) CsA was eliminated from 1 of the study treatments and Rapamune and CsA treatments were compared in the other 2 studies (207, 210).

8.2.1 Concentration Control in Studies 207 and 210

A formal study plan was prepared for the implementation of whole blood sirolimus concentration control in study 207, which included detailed instructions for adjusting Rapamune doses based on trough sirolimus concentrations at successive intervals (ie, trough concentrations during week 1, the full PK profile on day 7, trough concentrations during weeks 2 and 3, trough concentrations during weeks 4 to 8, and trough concentrations beyond week 9). The study plan for Rapamune dose individualization was also applied to study 210. In both studies, whole blood samples were sent to St. George's Hospital Medical School, London, UK, which provided analytical and PK advisory services to the investigators.

The data from studies 207 and 210 showed that trough concentrations were as efficient as full PK profiles on day 7 in individualizing Rapamune dose administration. This was not unreasonable, since the area under the curve during a 24-hour dose interval ($AUC_{0\text{-}24}$) is known to correlate well with the trough concentration during the 24-hour interval ($C_{min,24h}$) after administration of either oral solution[23] or tablet[58] formulations. Therefore, dose individualization in studies 212 and 310 was based on trough concentrations only.

8.2.2 Concentration Control in Studies 212 and 310

The methods used for the concentration control of sirolimus and CsA in studies 212 and 310 were presented in considerable detail in the clinical study reports (CSR-41764[59] and CSR-40858,[60] respectively). The dose regimens for the 2 studies were quite similar, but randomization times for the studies differed. For study 212, patient randomization occurred up to day 7 after transplant; for study 310, randomization occurred at 3 months after transplantation.

8.3 Individualization of Rapamune Doses

8.3.1 Estimation of Rapamune Maintenance and Loading Doses

The maintenance dose (MD) and loading dose (LD) used to adjust sirolimus concentrations in individual patients were estimated by the use of equations 1 and 2.

$$MD = \text{Current dose} \bullet C_{min,2}/C_{min,1} \qquad (1)$$

In equation (1), $C_{min,1}$ = current trough concentration (or average of more than 1 value), and $C_{min,2}$ = target trough concentration.

$$LD = R \bullet (MD_2 - MD_1) \qquad (2)$$

In equation 2, R = trough accumulation factor (R = 3 as previously determined),[61] MD_1 = current maintenance dose, and MD_2 = new maintenance dose.

8.3.2 Dose Adjustments to Achieve Target Concentrations of Sirolimus and CsA After Randomization in Study 310

Tables 8.3.2A and 8.3.2B provide the guidelines used for the individualization of Rapamune and CsA doses in patients undergoing progressive elimination of CsA in conjunction with concentration-controlled sirolimus.

TABLE 8.3.2A. GUIDELINES FOR RAPAMUNE DOSE ADJUSTMENTS IN STUDY 310 (IMx)

Topic	Comment[a]
Initial dose adjustment	• The average patient receiving a Rapamune regimen of 2 mg/day before randomization showed sirolimus trough levels of approximately 10 ng/mL. However, 80% of patients were within a range of approximately 5 to 15 ng/mL. • To most rapidly achieve a concentration within the target range of 20 to 30 ng/mL, both an LD and an MD were calculated for individual patients (see section 8.3.1). • The maximum Rapamune dose administered on any day was not to exceed 40 mg. If the total dose (LD + MD) exceeded 40 mg, the LD was to be administered over 2 days. • The calculated dose was rounded off to a prescribed dose, consisting of a predefined number of Rapamune tablets of different strengths.
Subsequent dose adjustments	• The initial calculated MDs for patients undergoing CsA elimination were to be administered for at least 1 to 2 weeks before assuming that the patient had reached a new whole blood sirolimus steady-state level. • If the new steady-state level was < 20 ng/mL, a new MD was calculated and administered. • If the new steady-state level was within the target of 20 to 30 ng/mL, further dose adjustments were not needed. • If the new steady-state level was > 30 ng/mL, a new MD was calculated and administered.
Important monitoring considerations	• Trough samples were to be collected between 20 to 24 hours after the previous dose. • The use of strong inhibitors of CYP3A4 and P-glycoprotein were not to be administered. If it was essential to administer such agents, however, sirolimus trough concentrations were to be carefully monitored. • If CsA doses were abruptly increased or decreased, sirolimus trough concentrations were to be carefully monitored. • If CsA was abruptly withdrawn, the daily dose of Rapamune was to be increased 4-fold. • Significant increases or decreases in Rapamune doses were to be verified by a check on compliance and the use of more than a single trough concentration.

IMx = instrumentation by Abbott Laboratories for detection of sirolimus by microparticle enzyme immunoassay, LD = loading dose, MD = maintenance dose, CsA = cyclosporine, CYP3A4 = cytochrome P450 isozyme 3A4.
a: The target range for patients with blood samples assayed by a chromatographic method was 16 to 24 ng/mL, which was equivalent a range of 20 to 30 ng/mL for samples assayed by the IMx method.

TABLE 8.3.2B. GUIDELINES FOR CsA DOSE WITHDRAWAL IN STUDY 310

Sirolimus Trough	Comment
< 20 ng/mL	• The dose of CsA was to be decreased by 25% on the day that the Rapamune LD was administered, by 50% within 1 week of randomization, and then completely between 4 and 6 weeks after randomization.
> 20 ng/mL	• The dose of CsA was to be decreased by 25% per week and then stopped completely between 4 and 6 weeks after randomization.

Abbreviations: CsA = cyclosporine, LD = loading dose.

8.3.3 Two-Stage Population Analysis of Pharmacokinetic Parameters (1 Year or Less and Greater Than 1 Year After Transplant)

The parameters included in the 2-stage population analysis were the time-normalized average trough concentrations ($C_{min,TN}$), average doses ($Dose_{TN}$), and dose-normalized average trough concentrations (DN-$C_{min,TN}$) in individual patients as defined by the following relationships:

$$C_{min,TN} = AUC_{0-t}/t \qquad (3)$$

In equation 3, $C_{min,TN}$ is the time-normalized average steady-state trough concentration; AUC_{0-t} is the area under trough concentration-time profile from the start of dose administration to time t.

$$Dose_{TN} = AUD_{0-t}/t \qquad (4)$$

In equation 4, $Dose_{TN}$ is the time-normalized average dose; AUD_{0-t} is the area under the dose curve from the start of dose administration up to time t.

$$DN\text{-}C_{min,TN} = C_{min,TN} \bullet DOSE_{TN}/NDOSE \qquad (5)$$

In equation 5, DN-$C_{min,TN}$ is the dose-normalized, time-normalized average steady-state trough concentration; NDOSE = 2 mg for Rapamune and 300 mg for CsA.

8.3.3.1 Assay Normalization Among Studies

Both the Abbott sirolimus immunoassay (IMx) testing system and chromatographic bioanalytical methods were used to assay whole blood sirolimus concentrations among studies presented in this report. Because of immunochemical cross-reactivity by metabolites, concentrations measured by IMx are higher than concentrations measured by chromatographic methods. The bias due to cross-reactivity has been shown to be approximately 25% for both the high-performance liquid chromatography (HPLC)/tandem mass spectrophotometry (MS/MS)[62] and HPLC with ultraviolet (UV) detection (HPLC/UV)[63] methods. Therefore, for purposes of PK analysis, the following relationship has been used to convert measured concentrations by chromatographic methods to concentrations by IMx:

$$\text{IMx assay (ng/mL)} = 1.25 \bullet \text{chromatographic assay (ng/mL)} \qquad (6)$$

All results presented in this report are expressed as IMx results or IMx equivalents using the above equation.

8.3.3.2 Summary of 2-Stage Population Analysis

Table 8.3.3.2A provides a summary of sirolimus PK characteristics ≤ 1 year and > 1 year after transplant for the administrations of sirolimus by dose control and concentration control.

TABLE 8.3.3.2A. COMPARATIVE SIROLIMUS PHARMACOKINETIC CHARACTERISTICS AFTER ADMINISTRATION OF SIROLIMUS BY DOSE CONTROL AND CONCENTRATION CONTROL

Time Period	Factor	Comment
≤ 1 Year after transplant	Control	• The ratios of the mean sirolimus $C_{min,TN}$, $Dose_{TN}$, and DN-$C_{min,TN}$ values for concentration control/dose control were approximately 2.1, 3.8, and 0.63, respectively. $C_{min,TN}$ was expected to increase since higher immunosuppressive sirolimus concentrations are required in the absence of CsA. The significantly higher $Dose_{TN}$ and lower DN-$C_{min,TN}$ values were expected because of the decreased bioavailability of sirolimus in the absence of CsA.
	Race	• During concentration control, $Dose_{TN}$ values were significantly larger (20%) and DN-$C_{min,TN}$ values were significantly lower (14%) in black patients (n = 17) than in nonblack patients. DN-$C_{min,TN}$ values were significantly lower (37%) in black patients (n = 20) during dose control. However, these results were based on a small sample size of black patients.
	Sex	• There were no statistically significant differences between male and female patients in sirolimus PK parameters.
	Study	• Statistically significant interstudy differences were observed for $C_{min,TN}$ and $Dose_{TN}$, which were anticipated based on study design differences.
> 1 Year after transplant	Control	• The ratios of the mean sirolimus $C_{min,TN}$, $Dose_{TN}$, and DN-$C_{min,TN}$ values for concentration control/dose control were approximately 2.1, 2.8, and 0.81, respectively. The $C_{min,TN}$ ratio agreed exactly with the ratio for the ≤ 1-year interval. However, $Dose_{TN}$ was significantly decreased and DN-$C_{min,TN}$ was significantly increased compared with the values for the ≤ 1-year interval. The differences in $Dose_{TN}$ and DN-$C_{min,TN}$ may have been expected due to the approximately 25% decrease in CsA doses during the > 1-year interval.
	Race	• During dose control, DN-$C_{min,TN}$ values in black patients (n = 38) were significantly lower (24%) than those in nonblack patients. There were no statistically significant differences in DN-$C_{min,TN}$ by race during concentration control.
	Sex	• During dose control, DN-$C_{min,TN}$ was significantly higher (16%) in male than in female patients, which did not appear to be clinically important. There was no difference between male and female patients in DN-$C_{min,TN}$ during concentration control.
	Study	• Statistically significant interstudy differences were observed for $C_{min,TN}$, $Dose_{TN}$, and DN-$C_{min,TN}$, which were expected based on study design differences.
≤ 1 Year vs > 1 Year after transplant	Time period	• Statistically significant differences were observed for $Dose_{TN}$ and DN-$C_{min,TN}$, which were due to significant differences among study, dose control, and race categories.

$C_{min,TN}$ = time-normalized average steady-state trough concentration, $Dose_{TN}$ = average time-normalized dose, DN-$C_{min,TN}$ = dose-normalized average trough whole blood concentration, CsA = cyclosporine, PK = pharmacokinetic.

8.4 Brief Summary of Pharmacokinetic and Pharmacodynamic Conclusions

8.4.1 Concentration-Effect Relationship During 75 Days After Transplant (Protocol 0468H1-310-GL)

A formal concentration-response analysis was conducted to determine the relationship between drug concentrations and efficacy. Drug concentrations and various demographic parameters were treated as independent variables. Acute rejection, as a measure of efficacy, was investigated by logistic regression using data for 2 months (up to 75 days). The estimated coefficient for drug exposure and the corresponding odds ratio and associated 95% confidence interval (CI) derived from logistic regression were evaluated for clinical meaningfulness.

8.4.2 Summary of Concentration-Effect Analyses

A summary of concentration-effect analyses, based on the relationship between acute rejection and explanatory variables, is summarized below.

- The final multivariate logistic regression model, based on data for 75 days after transplant, contained terms for dichotomized trough sirolimus concentrations, dichotomized trough CsA concentrations, sex, age, and age•HLA mismatch.

- Acute rejection was approximately 4.7 times more likely when sirolimus concentrations were below 5 ng/mL and 2.2 times more likely when CsA concentrations were below 150 ng/mL.

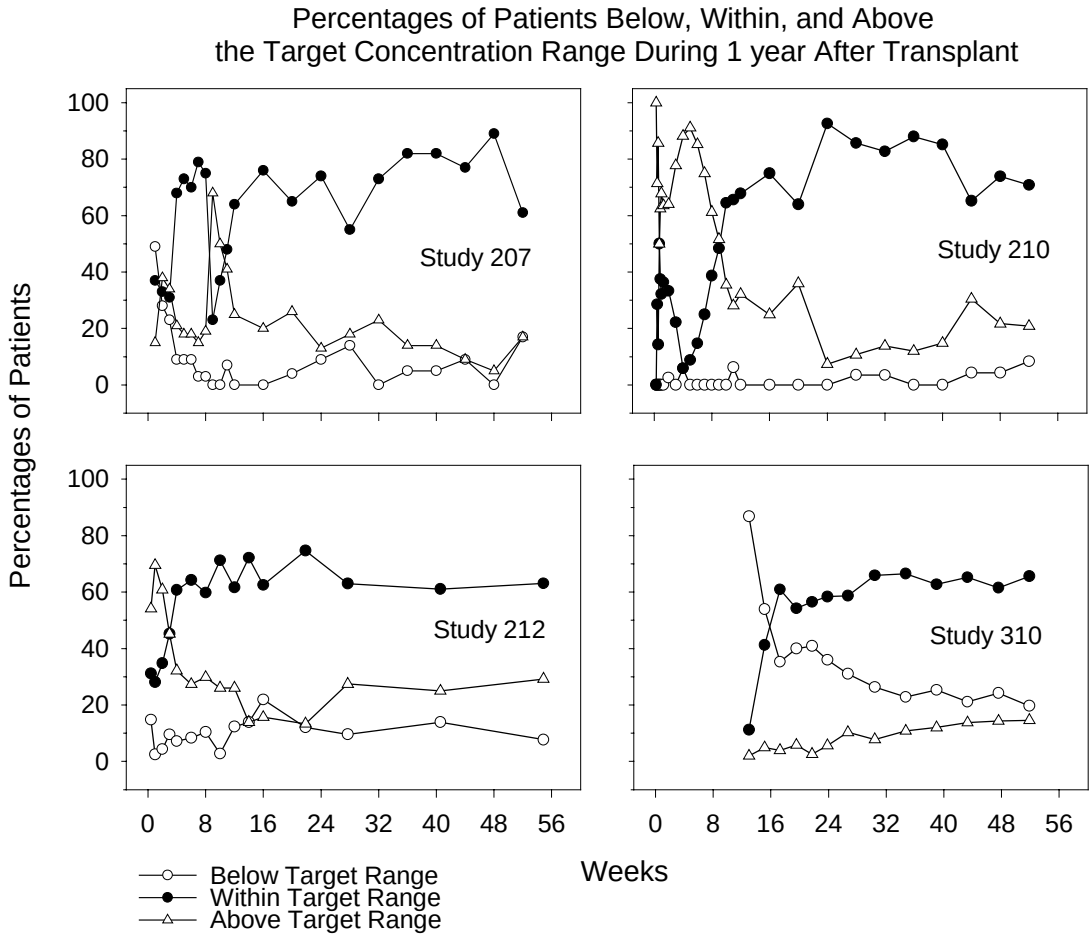
- The predicted probabilities of acute rejection were very close to the actual acute rejection rates, when sirolimus concentrations remain above 5 ng/mL and CsA concentrations either higher or lower than 150 ng/mL, regardless of sex.

8.5 Therapeutic Drug Monitoring of Sirolimus

8.5.1 Evaluation of Dose Algorithms From Sirolimus Concentration-Control Studies

The dose algorithm used in sirolimus concentration-control trials was evaluated by estimating the percentages of patients with sirolimus concentrations below, within, and above the sirolimus target concentration range. The concentration limits used in estimating the percentages included a factor of ± 10% to account for assay variability (ie, –10% at the lower limit and +10% at the upper limit). The time courses for the percentages of patients below, within, and above the target range are shown in Figure 8.5.1A for studies 207, 210, 212, and 310.

FIGURE 8.5.1A. PERCENTAGES OF PATIENT BELOW, WITHIN, AND ABOVE THE TARGET SIROLIMUS TROUGH CONCENTRATION RANGE DURING 1 YEAR AFTER TRANSPLANT IN CONCENTRATION-CONTROL STUDIES



The percentage-time profiles in Figure 8.5.1A show that the percentage of patients within the therapeutic windows (according to protocol) ≤ 1 year after transplant exceeded 60% for each of the 4 studies.

Table 8.5.1A provides a summary of the descriptive statistics for the average percentages of patients with sirolimus concentrations below, within, and above the target ranges during the first year for studies 207, 210, 212, and 310.

TABLE 8.5.1A. AVERAGE PERCENTAGES OF PATIENTS BELOW, WITHIN, AND ABOVE THE TARGET SIROLIMUS CONCENTRATIONS RANGES IN CONCENTRATION-CONTROL STUDIES ≤ 1 YEAR AFTER TRANSPLANT

Study	Target Range (ng/mL)	Time Interval (months)	Visits	Average Percentages (%) ± SD (min, max) Below Range	Within Range	Above Range
207	10 to 20	3 to 12	11	5.73 ± 5.93 (0, 17)	72.6 ± 10.3 (55, 89)	16.7 ± 6.6 (5, 26)
210	10 to 20	>2 to 12	13	2.33 ± 2.89 (0, 8.3)	75.5 ± 10.2 (64, 93)	22.2 ± 9.8 (7.4, 36)
212	10 to 20	1 to 12	11	10.9 ± 4.9 (2.7, 22)	64.9 ± 5.2 (60, 75)	24.2 ± 6.7 (13, 32)
310	20 to 30	>3 to 12	11	29.3 ± 7.6 (20, 41)	61.5 ± 4.2 (54, 66)	9.2 ± 4.3 (2.6, 15)
All	-	-	46	11.6 ± 11.8 (0, 41)	68.9 ± 9.7 (54, 93)	18.3 ± 9.1 (2.6, 36)

SD = standard deviation.

Among the 4 studies, 61.5% to 75.5% of patients had sirolimus concentrations within the target range, and 70.7% to 97.7% of patients had concentrations that were above the lower limit of the target concentration ranges. For the 4 studies combined, 68.9% of patients were within the target ranges, and 87.2% were above the lower limit of the target sirolimus concentration ranges. The results in Table 8.5.1A demonstrate the ability to achieve concentrations within a target range during sirolimus therapeutic drug monitoring (TDM).

8.5.2 Target Sirolimus Concentration Ranges for Therapeutic Drug Monitoring

The following discussion presents the rationale for the selection of sirolimus concentration ranges for TDM based on supportive data from statistical, pharmacodynamic (PD), and PK analyses.

8.5.2.1 Supportive Data From Statistical Analyses of Efficacy Endpoints

During the clinical development of Rapamune, efficacy data have been collected from dose-controlled (phase 3) and concentration-controlled (phase 2 and 3) studies in renal transplant recipients. In each of the studies, statistical analyses of the efficacy endpoints have shown that Rapamune is effective for the prophylaxis of acute rejection in renal allograft recipients. Tables 8.5.2.1A and 8.5.2.1B present summaries of the statistical analyses of efficacy endpoints among Rapamune clinical studies in renal transplant recipients for the dose-controlled and concentration-controlled studies, respectively.

TABLE 8.5.2.1A. SUMMARY OF THE STATISTICAL ANALYSES FOR SELECTED EFFICACY ENDPOINTS IN RAPAMUNE CLINICAL STUDIES IN RENAL TRANSPLANT RECIPIENTS AT 12 MONTHS (DOSE-CONTROLLED STUDIES)

Study	Comparison (A vs B)	Endpoint	Rate Difference (% A-B)	95% CI	p-Value
301	RAPA 2 mg vs AZA	Biopsy-confirmed acute rejection	-8.7	-17.2 to -0.1	0.0456[a]
		Graft survival	0.9	-3.6 to 5.5	0.674[b]
302	RAPA 2 mg vs placebo	Biopsy-confirmed acute rejection	-13.8	-23.6 to -4.0	0.0066[a]
		Graft survival	2.2	-4.7 to 9.1	0.597[b]
309	RAPA 2 mg: tablet vs oral solution	Biopsy-confirmed acute rejection	-1.8	-9.3 to 5.8	0.665[b]
		Graft survival	-3.3	-8.6 to 2.0	0.278[b]

RAPA = sirolimus, AZA = azathioprine, CI = confidence interval.
a: Cochran-Mantel-Haenszel p-value.
b: Fisher's exact test.

TABLE 8.5.2.1B. SUMMARY OF THE STATISTICAL ANALYSES FOR EFFICACY ENDPOINTS IN RAPAMUNE CLINICAL STUDIES IN RENAL TRANSPLANT RECIPIENTS (CONCENTRATION-CONTROLLED STUDIES)

Study	Comparison[a] (A vs B)	Endpoint[b]	Interval (month)	Rate Difference (% A-B)	95% CI	p-Value
310	CsA + RAPA 2 mg vs RAPA	Graft survival	12	-1.4	-4.9 to 2.1	-
		Biopsy-confirmed acute rejection	12	Mild (9.7) Mod. (-8.6) Severe (-1.3)	-	0.514[c]
212	CsA + RAPA 2 mg vs RAPA	Serum creatinine	12	20.3[d] (169.9 vs 135.4 µmol/L)	-	0.002[e]
		Biopsy-confirmed acute rejection	12	- 3.4	-7.8 to 14.7	0.598[f]
207	RAPA + AZA vs CsA + AZA	Biopsy-confirmed acute rejection	1	10.4	-9.8 to 30.7	
			12	3.4	-17.7 to 24.4	
		Treatment failure	1	3.4	-17.7 to 24.4	
		Graft survival	12	7.5	-	-
210	RAPA + MMF vs CsA + MMF	Biopsy-confirmed acute rejection	1	7.1	-6.9 to 21.1	-
			12	9.1	-9.4 to 27.6	
		Treatment failure	1	12.1	-3.0 to 27.2	
		Graft survival	12	2.5	-	-

CI = confidence interval, CsA = cyclosporine, RAPA = Rapamune, AZA = azathioprine, MMF = mycophenolate mofetil.
a: Sirolimus was concentration controlled.
b: Treatment failure included the occurrence of either biopsy-confirmed acute rejection, graft loss, death, or discontinuation from study treatment.
c: Cochran-Mantel-Haenszel p-value.
d: Percentage change from group mean, computed as (RAPA + CsA mean – RAPA mean)/RAPA + CsA mean x 100%.
e: t Test.
f: Fisher's exact test.

Overall, the data presented in Tables 8.5.2.1A and 8.5.2.1B indicate that sirolimus was effective at concentrations used in clinical phase 2 and 3 studies for the prophylaxis of acute rejection, when used either by dose control in combination with CsA or when used by concentration control after withdrawal of CsA. However, actual trough sirolimus concentrations that were measured in individual patients after the oral administration of Rapamune formulations (oral solution and tablet) exhibited great variability within and between subjects. Multivariate logistic regression of acute rejection versus explanatory variables has shown a direct relationship between acute rejections rates and drug concentrations. It is therefore important to define a therapeutic window that will decrease the probability of acute rejections.

8.5.2.2 Supportive Pharmacodynamic Analyses From Dose-Controlled Studies

The results from multivariate logistic regression analysis of acute rejection versus explanatory variables showed that the rejection rates in renal allograft patients over 75 days after transplant were greatly increased when whole blood sirolimus concentrations were < 5 ng/mL. Table 8.5.2.2A lists the odds ratios for average whole blood sirolimus based on dichotomized drug concentrations. The parameters for CsA are also included for comparison.

TABLE 8.5.2.2A. ODDS RATIOS FOR WHOLE BLOOD SIROLIMUS AND CsA CONCENTRATIONS BASED ON MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

	Sirolimus		CsA	
Studies	Dichotomized Concentration (ng/mL)	Odds Ratio	Dichotomized Concentration (ng/mL)	Odds Ratio
301/302 Combined[64]	3.5	5.26	260	3.07
310	5	4.72	150	2.18

CsA = cyclosporine.

For the combined analysis of studies 301 and 302, drug concentrations were dichotomized at the upper limit of the first quartile. For study 310, drug concentrations were arbitrarily dichotomized at 5 ng/mL for sirolimus and 150 ng/mL for CsA. Overall, the results in Table 8.5.2.2A show that the rejection rate was at least approximately 4.7 times higher when sirolimus concentrations were < 5 ng/mL. Similarly, when CsA concentrations were below 150 ng/mL, the rejection rate increased by 2.2-fold.

Distribution frequency analysis of clinical laboratory data during combined Rapamune and CsA administration suggested that clinically important effects on certain laboratory outcomes (eg, platelet count, cholesterol, and triglycerides) tended to occur more frequently during the first 6 months after transplant when sirolimus concentrations were greater than approximately 15 ng/mL.

The outcomes of the PD analysis suggest a therapeutic window of 5 to 15 ng/mL in patients receiving Rapamune doses of 2 mg/day during combined therapy with CsA and steroids.

Supportive data were not available for the PD modeling of acute rejection rates following CsA withdrawal.

8.5.2.3 Supportive Pharmacokinetic Data From Previous Dose-Controlled Studies

In previous dose-controlled pivotal trials for Rapamune oral solution and Rapamune tablets, it was shown that the 10th and 90th percentiles for sirolimus $C_{min,TN}$ were very similar regardless of study or formulation after nominal 2-mg/day oral doses of Rapamune.

Table 8.5.2.3A lists the 10th and 90th percentiles for sirolimus $C_{min,TN}$ and DN-$C_{min,TN}$ by study and formulation for previous dose-controlled pivotal phase 3 trials in renal transplant recipients.

TABLE 8.5.2.3A. PERCENTILES FOR AVERAGE SIROLIMUS TROUGH CONCENTRATIONS (DAYS 2 TO 360) FROM DOSE-CONTROLLED PIVOTAL PHASE 3 TRIALS IN RENAL TRANSPLANT RECIPIENTS

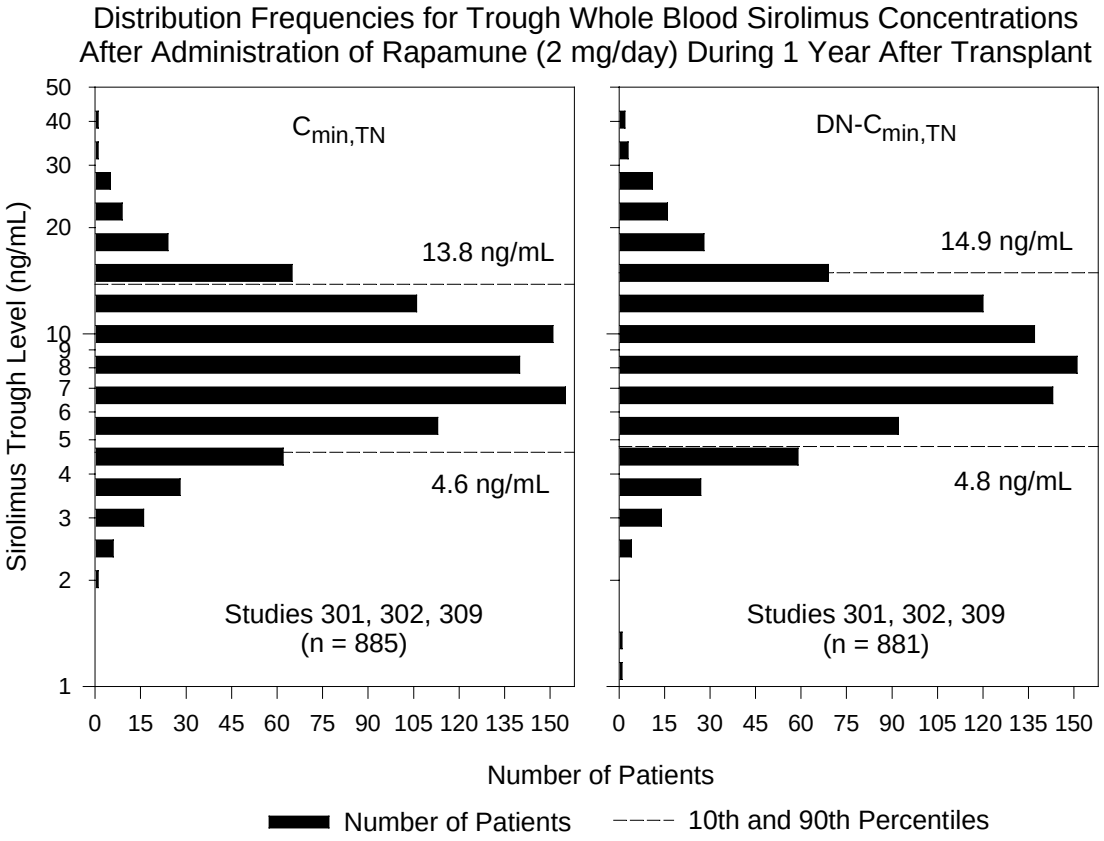
		----------$C_{min,TN}$----------			----------DN-$C_{min,TN}$----------		
Study	Formulation	n	10th	90th	n	10th	90th
301	Oral solution	265	4.70	13.7	265	5.04	15.4
302	Oral solution	213	4.09	12.5	209	4.39	14.1
309	Oral solution	197	4.56	13.4	197	4.40	14.3
309	Tablet[a]	210	5.23	14.9	210	5.11	15.1
All combined	Oral solution/tablet	885	4.58	13.8	881	4.76	14.9

$C_{min,TN}$ = time-normalized average steady-state trough concentration,
DN-$C_{min,TN}$ = dose-normalized average trough whole blood concentration.
a: Rapamune 1-mg oval tablet.

The data in Table 8.5.2.3A show that among 885 patients in 4 pivotal phase 3 trials, the 10th and 90th percentiles for DN-$C_{min,TN}$ were 4.76 and 14.9, respectively. Therefore, the average sirolimus trough concentrations in 80% of patients fall within a window of approximately 5 to 15 ng/mL after administration of either Rapamune oral solution or Rapamune tablets. These results agree with the conclusions based on the PD analysis of data from the Rapamune dose-controlled studies.

Figure 8.5.2.3A shows a comparison of the distributions of sirolimus actual ($C_{min,TN}$) and dose-normalized (DN-$C_{min,TN}$) trough concentrations after dose-controlled Rapamune administration (2 mg/day) during the first year after transplant.

FIGURE 8.5.2.3A. COMPARISON OF THE DISTRIBUTIONS OF SIROLIMUS $C_{min,TN}$ AND DN-$C_{min,TN}$ AFTER DOSE-CONTROLLED RAPAMUNE ADMINISTRATION (2 mg/day) DURING ≤ 1 YEAR AFTER TRANSPLANT



8.5.2.4 Supportive Pharmacokinetic Data From Current Concentration-Controlled Studies

Table 8.5.2.4A provides the descriptive statistics for average sirolimus PK parameters ($C_{min,TN}$, $Dose_{TN}$, and DN-$C_{min,TN}$) by time interval (≤ 1 year, > 1 year) for sirolimus concentration control studies. The data for dose-control treatments in these studies are also included for comparison with the previous dose-controlled trials.

TABLE 8.5.2.4A. COMPARISON OF THE AVERAGE SIROLIMUS PHARMACOKINETIC PARAMETERS ≤ 1 YEAR AND > 1 YEAR AFTER TRANSPLANT

Sirolimus Control	Duration	Studies	n	Statistic	$C_{min,TN}$ (ng/mL)	$Dose_{TN}$ (mg/day)	DN-$C_{min,TN}$ (ng/mL)
Concentration	≤ 1 year	207, 210, 212, 310	347	Mean	20.2	6.89	5.85
				Median	20.6	7.13	5.93
				10th pct	13.8	3.69	3.20
				90th pct	28.4	12.5	11.0
	> 1 Year	207, 210, 212, 310, 306, 311	161	Mean	19.8	5.69	6.95
				Median	20.0	6.00	7.01
				10th pct	13.9	3.00	3.92
				90th pct	28.4	10.00	13.00
Dose	≤ 1 Year	212, 310	293	Mean	9.17	1.94	9.44
				Median	9.24	2.00	9.48
				10th pct	5.52	1.37	5.27
				90th pct	15.6	2.32	16.4
	> 1 Year	212, 310, 306, 311	298	Mean	9.10	2.11	8.63
				Median	9.27	2.00	8.63
				10th pct	5.14	1.39	4.72
				90th pct	15.5	3.63	15.2

$C_{min,TN}$ = time-normalized average steady-state trough concentration, $Dose_{TN}$ = average time-normalized dose, DN-$C_{min,TN}$ = dose-normalized average trough whole blood concentration, pct = percentile.

The results in Table 8.5.2.4A for concentration-controlled trials show that the 10th and 90th percentiles for average whole blood sirolimus concentrations ($C_{min,TN}$) were approximately 14 ng/mL and 28 ng/mL, respectively, regardless of time interval (≤ 1 year versus > 1 year). Therefore, a conservative estimate of the trough sirolimus therapeutic window during the concentration control of sirolimus administration without combined CsA administration would be 15 to 25 ng/mL.

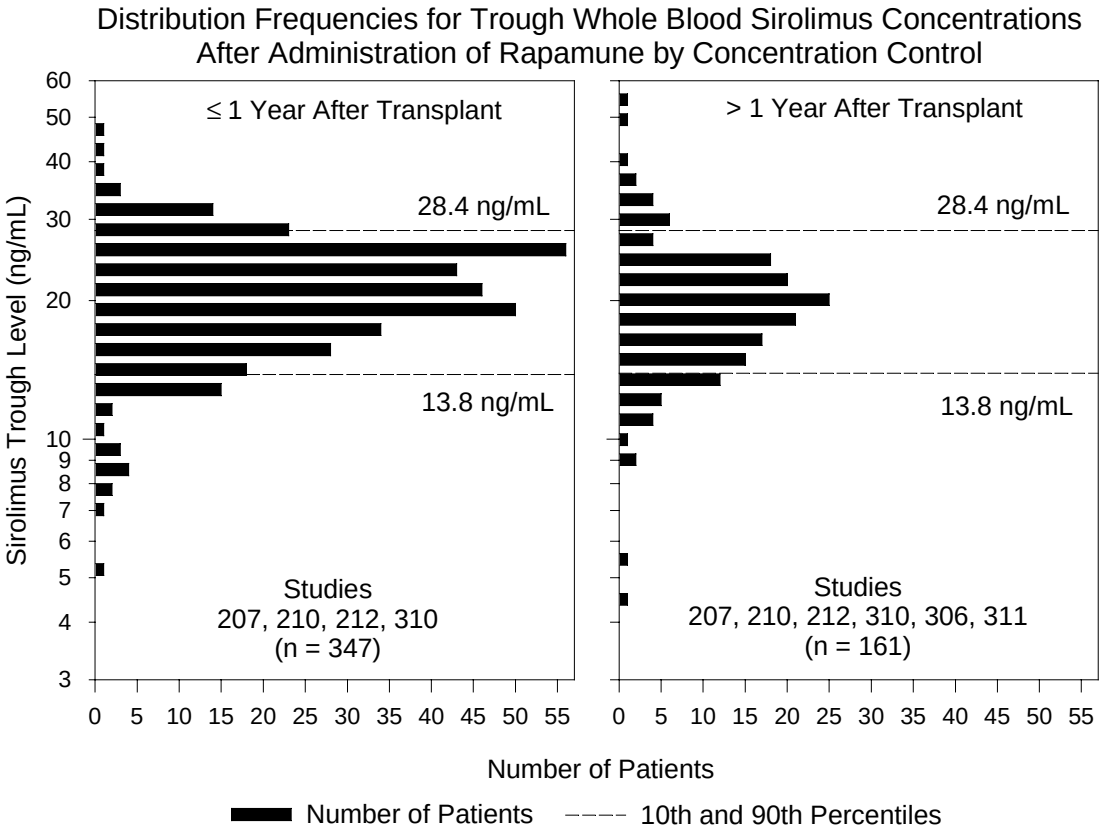
The data in Table 8.5.2.4A also show that the 10th and 90th percentiles for DN-$C_{min,TN}$ within the dose-controlled treatments of the studies were very similar to those for the previous phase 3 dose-controlled studies regardless of time period (5.27, 16.4 ≤ 1 year after transplant and 4.72, 15.2 > 1 year after transplant).

A review of the average Rapamune doses ($Dose_{TN}$) in Table 8.5.2.4A shows that the 10th and 90th percentiles ≤ 1 year after transplant were 3.69 mg/day and 12.5 mg/day, respectively. During the interval > 1 year, the 10th and 90th percentiles for sirolimus $Dose_{TN}$ were 3.00 mg/day and 10.0 mg/day, respectively. The median value of $Dose_{TN}$ for concentration

control was at least 3-fold greater than $Dose_{TN}$ for dose control (ie, 7.13 mg/day versus 2 mg/day during the first year; 6 mg/day versus 2 mg/day at > 1 year).

Figures 8.5.2.4A illustrate the distribution of trough whole blood sirolimus concentrations after concentration-controlled administration at the time intervals of ≤ 1 year and > 1 year after transplant.

FIGURE 8.5.2.4A. DISTRIBUTION FREQUENCIES FOR TROUGH WHOLE BLOOD SIROLIMUS CONCENTRATIONS AFTER ADMINISTRATION OF SIROLIMUS BY CONCENTRATION CONTROL



The use of the 10th and 90th percentiles for sirolimus trough concentrations in renal transplant recipients provides a convenient way of setting the upper and lower limits of the therapeutic window that includes 80% of patients.

Also, the same therapeutic window can be used for both sirolimus oral solution and sirolimus tablets. This conclusion is based on (1) the clinical equivalence of the 2 formulations in renal

transplant recipients during dose-controlled administration in study 309,[58] (2) the similar rates of acute rejection obtained during concentration-controlled administration in studies 212 (solution) and 310 (tablet; see Table 8.5.2.1B), and (3) the similarity in trough concentrations for a given dose.

8.5.3 Summary of Therapeutic Drug Monitoring

Table 8.5.3A provides a summary of phase 2 and 3 experience with the whole blood sirolimus concentration monitoring in renal allograft patients and recommendations for the TDM during dose-controlled and concentration-controlled administration of Rapamune formulations.

TABLE 8.5.3A. A SUMMARY OF PHASE 2 AND 3 EXPERIENCE WITH THE WHOLE BLOOD SIROLIMUS CONCENTRATION MONITORING IN RENAL ALLOGRAFT PATIENTS AND RECOMMENDATIONS FOR THE THERAPEUTIC DRUG MONITORING

TDM	Topic	Comments
Early experience with TDM	Achieving/maintaining target concentrations (studies 207, 210, 212, and 310)	• The percentage of patients within the target concentrations ranged from approximately 62% to 76%. • The percentages of patients above the lower limit of the target range ranged from approximately 71% to 98%. • The data indicate that sirolimus concentration control was demonstrated.
Basis for sirolimus TDM	Analysis of efficacy endpoints (studies 301, 302, 309, 212, 310, 207, and 210)	• Statistical analyses of efficacy endpoints in dose-controlled and concentration-controlled clinical trials demonstrate that sirolimus was effective at the concentrations achieved.
	PD modeling (301, 302, 310)	• Multivariate logistic regression of acute rejection and frequency distribution analysis of clinical laboratory values suggest a greater rate of acute rejection below 5 ng/mL and greater toxicity above 15 ng/mL after sirolimus dose-controlled administration.
	PK data (studies 301, 302, 309, 212, 310, 207, and 210)	• Among 885 patients from previous dose-controlled trials, sirolimus DN-$C_{min,TN}$ values of 80% of patients fell within the concentration range of 5 to 15 ng/mL, which agreed with the results from PD modeling. • Among 347 patients (≤ 1 year) and 161 patients (> 1 year) in current sirolimus concentration-controlled studies, $C_{min,TN}$ values of 80% of patients fell within a range of 14 to 28 ng/mL. A conservative therapeutic range for the concentration-controlled administration of sirolimus without CsA is 15 to 25 ng/mL. • The median value of $Dose_{TN}$ for concentration control was at least 3-fold greater than $Dose_{TN}$ for dose control (ie, 7.13 mg/day vs 2 mg/day at ≤ 1 year; 6 mg/day vs 2 mg/day at > 1 year).
Sirolimus TDM ranges	Dose control with combined CsA administration	• 5 to 15 ng/mL at a median dose of 2 mg/day for either Rapamune oral solution or Rapamune tablets.
	Concentration control without CsA administration	• 15 to 25 ng/mL at a median dose of approximately 7 mg/day at ≤ 1 year and 6 mg/day at > 1 year for either Rapamune oral solution or tablets.

TDM = therapeutic drug monitoring, PD = pharmacodynamic, PK = pharmacokinetic,
DN-$C_{min,TN}$ = dose-normalized average trough whole blood concentration,
$C_{min,TN}$ = time-normalized average steady-state trough concentration,
$Dose_{TN}$ = average time-normalized dose, CsA = cyclosporine.

9 RISK/BENEFIT SUMMARY AND CONCLUSION

Significant advances have been made in organ transplantation in the past decade. With the advent of new immunosuppressive agents, rates of acute rejection and short-term graft survival have improved. However, most of these drugs are associated with adverse events that limit the doses that can be used, in some cases requiring cessation of therapy. Examples of such toxicities include 1) nephrotoxicity, diabetes, and hypertension associated with the calcineurin inhibitors and 2) leukopenia and gastrointestinal side effects observed with the antiproliferative agents. As a result, the current trend in transplantation is to individualize treatment in order to identify optimal combination therapy that minimizes toxicity while maintaining efficacy.

Rapamune (sirolimus) is an efficacious immunosuppressive agent with a distinct mechanism of action and a toxicity profile that is generally distinct from that of other immunosuppressive drugs. Two (2) large-scale blinded studies evaluated the safety and efficacy of Rapamune in combination with CsA and corticosteroids for renal transplant patients. In 1 study (0468E1-301-US) Rapamune was compared with azathioprine; the other study (0468E1-302-GL) was placebo controlled. The results of these studies were consistent and showed that Rapamune treatment was associated with a significant reduction in the rate of acute rejection, including high-grade acute rejection. The rejection rates observed in these trials were similar to some of the lowest reported in the literature. The patient and graft survival rates were excellent. Two (2) main toxicities were identified: hyperlipidemia and exacerbation of CsA nephrotoxicity.

The evidence to date suggests that the renal dysfunction can best be palliated with reduction or elimination of CsA, because Rapamune itself shows no evidence of nephrotoxicity. Preclinical animal study results, as well as results of phase 2 trials in both patients with and those without transplants, have confirmed that Rapamune administered without CsA has no deleterious effect on GFR, even at high doses.

These findings led to the development of the immunosuppressive strategy that was tested in a controlled fashion in studies 310 and 212. Rapamune was combined with CsA and corticosteroids for the initial 3 months to minimize the rate of acute rejection during the immunologic high-risk period. CsA was then eliminated from the regimen to optimize long-term graft function.

The use of CsA (and tacrolimus) clearly has improved short-term graft survival significantly over the last 2 decades. However, long-term graft survival remains suboptimal, with the most

common causes of graft loss being death with a functioning graft and chronic allograft nephropathy (CAN). CAN is a nonspecific pathologic entity that can be the end result of a variety of immune (such as chronic rejection) and nonimmune insults (such as hypertension and drug toxicity).

In the view of experts in the transplant community, a main reason why the significant improvements in short-term graft survival have not translated into equally promising benefits long-term is that CsA and tacrolimus are both associated with chronic nephrotoxicity and hypertension. The nephrotoxicity is caused, in part, by hypoperfusion of the glomerulus, leading to ischemia and reduced GFR. Although initially reversible, long-term ischemia and other direct insults induced by CsA (such as up-regulation of transforming growth factor β) lead to irreversible interstitial fibrosis. The precise incidence of CsA-associated chronic nephropathy is difficult to ascertain. However, in studies of patients with liver and heart transplants who were treated with CsA, approximately 5% to 7% of patients actually progressed to end-stage renal disease requiring dialysis; chronic renal insufficiency was encountered much more frequently.[65,66,67,68]

Hence, there is clearly a clinical need for a regimen in which long-term exposure to the calcineurin inhibitors is minimized while immunosuppressive efficacy is maintained.

The regimen of concentration-controlled sirolimus with CsA elimination offers one such regimen. The rates of acute rejection are minimized by combining Rapamune with CsA for the initial (immunologic) high-risk period. Data from trials 301, 302, 310, and 212 have confirmed that this combination is highly effective in preventing acute rejection. Results from trials 310 and 212 further demonstrate that CsA can be safely eliminated after 2 to 4 months with Rapamune and steroids continued as the major immunosuppressants. The data, summarized in this document, showed that the above mentioned regimen, compared with the regimen of Rapamune and standard-dose CsA, is associated with the following:

- Comparable rates of acute rejection.
- Similar 1-year patient and graft survival.
- Significantly better renal function.
- Lower blood pressure.
- Lower rate of CsA-associated toxicities.

- Similar cholesterol levels (after treatment with lipid-lowering agents), despite much higher sirolimus concentrations.
- Similar rates of infection.

The main adverse events associated with Rapamune include thrombocytopenia and hyperlipidemia. The thrombocytopenia is generally mild and reversible with dose reduction or discontinuation of Rapamune. The majority of patients responded to pharmacologic and nonpharmacologic therapies for elevated cholesterol and triglyceride levels. For patients with severe or resistant hyperlipidemia, discontinuation of Rapamune results in improvements. Furthermore, 31% to 50% of the patients at month 12 had elevated HDL levels.

In conclusion, the data presented demonstrate that a regimen of concentration-controlled sirolimus with CsA elimination (after months 2 to 3) offers effective immunotherapy with distinct safety advantages over traditional CsA-based therapy. In contrast to CsA-based therapy, this regimen does not adversely affect GFR, cause hypertension, or induce interstitial fibrosis. These facts along with the finding that low rates of acute rejection were maintained should translate into improvement in long-term graft survival and lower rates of CAN. This regimen can be recommended for the majority of patients undergoing renal transplantation in the United States. The limited data on black patients do not allow any definitive recommendations to be made for this population.

10 REFERENCES

[1] Vezina C, Bolduc C, Kudelski A, Sehgal SN. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J Antibiot*. 1975;2:721-726.

[2] Sehgal SN, Baker H, Vezina C. Rapamycin (AY-22,989) a new antifungal antibiotic II. Fermentation, isolation and characterization. *J Antibiot*. 1975;28:727-732.

[3] Calne RY, Collier D, Lim S, et al. Rapamycin for immunosuppression in organ allografting. *Lancet*. 1989;2:227.

[4] Spencer-Briggs D, Collier DS, Chang JY. Effect of rapamycin on experimental renal transplantation in the baboon. Wyeth-Ayerst GTR-19079, 1990.

[5] Chen H, Wu J, Xu D, Luo H, Daloze PM. Reversal of ongoing heart, kidney, and pancreas allograft rejection and suppression of accelerated heart allograft rejection in the rat by rapamycin. *Transplantation*. 1993;56:661-666.

[6] Morris R, Wang J, Gregory C, Zheng B. Initial studies of the efficacy and safety of rapamycin RPM administered to cynomolgus monkey recipients of heart allografts. *J Heart Lung Transplant*. 1992;10:182.

[7] Sehgal SN, Molnar-Kimber K, Ocain TD, Weichman BM. Rapamycin: a novel immunosuppressive macrolide. *Med Res Rev*. 1994;14:1-22.

[8] Seghal SN. Rapamune, (RAPA, rapamycin, sirolimus): Mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. Wyeth-Ayerst GTR-31712, 1997.

[9] Liu J, Farmer JD Jr, Lane WS, Friedman J, Weissman I, Schreiber SL. Calcineurin is a common target of cyclophilin-cyclosporin A and FKBP-FK506 complexes. *Cell*. 1991;66:807-815.

[10] Liu J, Albers MW, Wandless TJ, et al. Inhibition of T cell signaling by immunophilin-ligand complexes correlates with loss of calcineurin phosphatase activity. *Biochemistry*. 1992;31:3896-3901.

[11] Flanagan WM, Corthesy B, Bram RJ, Crabtree GR. Nuclear association of a T cell transcription factor blocked by FK506 and cyclosporin A. *Nature*. 1992;352:803-807.

[12] McCaffrey PG, Perrino BA, Soderling TR, Rao A. NF-ATp, a T lymphocyte DNA-binding protein that is a target for calcineurin and immunosuppressive drugs. *J Biol Chem*. 1993;268:3747-3752.

[13] Terada N, Lucas JJ, Szepesi A, Franklin RA, Domenico J, Gelfand EW. Rapamycin blocks cell cycle progression of activated T cells prior to events characteristic of the middle to late G_1 phase of the cycle. *J Cell Physiol*. 1993;154:7-15.

[14] Jefferies HBJ, Reinhard C, Kozma SC, Thomas G. Rapamycin selectively represses translation of the "polypyrimidine tract" mRNA family. *Proc Natl Acad Sci USA*. 1994;91:4441-4445.

[15] Jefferies HBJ, Fumagalli S, Dennis PB, Reinhard C, Pearson RB, Thomas G. Rapamycin suppresses 5'TOP mRNA translation through inhibition of p70 (S6k). *EMBO J*. 1997;16:3693-3704.

[16] Terada N, Patel HR, Takase K, Kohno K, Nairn AC, Gelfand EW. Rapamycin selectively inhibits translation of mRNAs encoding elongation factors and ribosomal proteins. *Proc Natl Acad Sci USA.* 1994;91:11477-11481.

[17] Beretta L, Gingras AC, Svitkin YV, Hall MN, Sonenberg N. Rapamycin blocks the phosphorylation of 4E-BP1 and inhibits cap-dependent initiation of translation. *EMBO J.* 1996;15:658-664.

[18] Feuerstein N, Huang D, Prystowsky MB. Rapamycin selectively blocks interleukin-2-induced proliferating cell nuclear antigen gene expression in T lymphocytes: evidence for inhibition of CREB-ATF binding activities. *J Biol Chem.* 1995;270:9454-9458.

[19] Lai JH, Tan H. CD28 signaling causes a sustained down-regulation of I kappa B alpha which can be prevented by the immunosuppressant rapamycin. *J Biol Chem.* 1994;269:30077-30080.

[20] Nourse J, Firpo E, Flanagan WM, et al. Interleukin-2-mediated elimination of the p27Kip1 cyclin-dependent kinase inhibitor prevented by rapamycin. *Nature.* 1994;372:570-573.

[21] Sehgal SN, Camardo JS, Scarola JA, Maida BT. Rapamycin (sirolimus, Rapamune). *Curr Opin Nephrol Hypertens.* 1995;4:482-487.

[22] Kahan BD, Julian BA, Pescovitz MD, et al. Sirolimus reduces the incidence of acute rejection episodes despite lower cyclosporine doses in Caucasian recipients of mismatched primary renal allografts: a phase II trial. *Transplantation.* 1999;68(10):1526-1532.

[23] Fawl R, Goldberg-Alberts R, Zimmerman J. A double-blind, comparative study of the effect of two dose levels of sirolimus versus azathioprine, administered concomitantly with standard immunosuppressive therapy in renal allograft recipients: 6-month report (protocol 0468E1-301-US). Wyeth-Ayerst GMR-32348, 1999.

[24] DeLoskey R, Goldberg-Alberts R, Zimmerman J, Caulfield M. A placebo-controlled, double-blind study of the effect of two dose levels of sirolimus plus standard immunosuppressive therapy in renal allograft recipients: 6-month report (protocol 0468E1-302-GL). Wyeth-Ayerst GMR-33147, 1999.

[25] Groth CG, Bäckman L, Morales JM, et al. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group. *Transplantation.* 1999;67(7):1036-1042.

[26] Kreis H, Cisterne JM, Land W, et al. Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. *Transplantation.* 2000;69(7):1252-1260.

[27] Nankivell BJ, Gruenewald SM, Allen RDM, Chapman JR. Predicting glomerular filtration rate after kidney transplantation. *Transplantation*. 1995;59:1683-1689.

[28] National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel II). *Circulation*. 1994;89:1329-1445.

[29] Fredrickson DS. An international classification of hyperlipidemias and hyperlipoproteinemias. *Ann Intern Med*. 1971;75:471-472.

[30] Zimmerman JJ. A two-stage population analysis of pharmacokinetic parameters from the sirolimus phase I, II, and III studies. Wyeth-Ayerst GTR-34557, 1998.

[31] Zengh J, Sambol NC, Zimmerman J, Zaidi A. Population pharmacokinetics (PK) of sirolimus. *Clin Pharmacol Ther*. 1996; 59(Suppl 2):S150. Abstract.

[32] Zimmerman JJ, Gage AT, DiLea C. Dose proportionality of sirolimus (rapamycin) in stable renal transplant recipients: final report (protocol 468E1-117-US). Wyeth-Ayerst GMR-26931, 1998.

[33] Arnold J, Gurr JA, Goldberg-Alberts R, Flynn A, Jaffe JS, Zimmerman JJ. A double-blind, comparative study of the effect of two dose levels of sirolimus versus azathioprine, administered concomitantly with standard immunosuppressive therapy in renal allograft recipients: 6-month report (protocol 0468E1-301-US). Wyeth-Ayerst GMR-32348, 1998.

[34] Howell RS, Scatina JA, Sisenwine SF. The distribution of radiolabeled rapamycin within human whole blood. Wyeth-Ayerst GTR-22348, 1993.

[35] Leung LY, Zimnmerman JJ, Lim HK. Rapamycin (sirolimus): biotransformation in healthy male subjects after a single oral dose of the ^{14}C-radiolabeled drug (nominal 40 mg). Wyeth-Ayerst GTR-29528, 1997.

[36] DiCioccio AT, Leung L. Rapamycin (sirolimus): mass balance and excretion of radioactivity following a single oral dose of ^{14}C-rapamycin (42 mg) in healthy male subjects. Wyeth-Ayerst GTR-26642, 1996.

[37] Lampen A, Zhang Y, Hackbarth I, Benet L, Sewing K-F, Christians U. Metabolism and transport of the macrolide immunosuppressant sirolimus in the small intestine. *J Pharm Exp Ther*. 1998;285:1104-1112.

[38] Sattler M, Guengerich FP, Yun C-H, Christians U, Sewing K-F. Cytochrome P-450 3A enzymes are responsible for biotransformation of FK506 and rapamycin in man and rat. *Drug Metab Dispos*. 1992;20:753-761.

[39] Crowe A, Lemaire M. In vitro and in situ absorption of SDA-RAD using a human intestinal cell line (Caco-2) and a single pass perfusion model in rats: comparison with rapamycin. *Pharmaceut Res*. 1998;15:1666-1672.

[40] Zimmerman JJ. Two-stage population analysis of whole blood sirolimus pharmacokinetic parameters from phase I, II, and III studies after administration of Rapamune Oral Solution and Rapamune Tablets (1-mg oval). Wyeth-Ayerst RPT-42893, 2001.

[41] Zimmerman JJ, Miller MJ, Burke JT. A dose proportionality study of 5- to 40-mg single doses of sirolimus oral tablets in healthy volunteers: final report (protocol 0468H1-166-EU). Wyeth-Ayerst GMR-32419, 1999.

[42] Zimmerman JJ, Kahan BD. Pharmacokinetics of sirolimus in stable renal transplant patients after multiple oral dose administration. *J Clin Pharmacol*. 1997;37:405-415.

[43] Zimmerman JJ, Meloni FJ, Maida B. A randomized, double-blind, placebo-controlled study of the safety, tolerance, and preliminary pharmacokinetics of ascending single doses of orally administered sirolimus (rapamycin) in stable renal transplant recipients: final report (protocol 0468E-111-US). Wyeth-Ayerst GMR-26832, 1996.

[44] Zimmerman JJ, Ferron GM, Lim H-K, Parker V. The effect of a high-fat meal on the oral bioavailability of the immunosuppressant sirolimus (rapamycin). *J Clin Pharmacol*. 1999;39:1155-1161.

[45] Zimmerman JJ, Miller MJ, DiLea C. The influence of a high-fat meal on the bioavailability of sirolimus from oral tablets in healthy subjects: final report (protocol 0468H1-172-US). Wyeth-Ayerst GMR-31331, 1999.

[46] Leister CA, Lewis I, DiLea C. A comparative bioavailability study of sirolimus administered with orange juice, Tang, and water in healthy subjects: final report (protocol 0468E1-146-US). Wyeth-Ayerst GMR-27610, 1998.

[47] Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, et al. Mechanisms of enhanced oral availability of CYP3A4 substrates by grapefruit constituents. *Drug Metab Dispos.* 1997;25:1228-1233.

[48] Zimmerman JJ, Gurr JA, DiLea C. Ascending single-dose safety, tolerance and pharmacokinetic study of oral sirolimus solution in pediatric patients with stable chronic renal failure receiving hemodialysis or peritoneal dialysis: final report (protocol 0468E1-147-US). Wyeth-Ayerst GMR-31333, 1998.

[49] Gurr JA, Miller M, Wickersham P, Goldberg-Alberts R, Bartusiak D, Zimmerman JJ. A placebo-controlled, double-blind study of the effect of two dose levels of sirolimus plus standard immunosuppressive therapy in renal allograft recipients: 6-month report (protocol 0468E1-302-GL). Wyeth-Ayerst GMR-33147, 1998.

[50] Lewis I, Li Y, Goldberg-Alberts R, Zimmerman JJ, Wade M. A comparative study of the effect and equivalence of sirolimus oral liquid versus sirolimus tablets, administered concomitantly with cyclosporine and corticosteroids in renal allograft recipients: 12-month report (protocol 0468E1-309-GL). Wyeth-Ayerst CSR-41034, 2000.

[51] Zimmerman JJ, Meloni FJ, DiLea C. Pharmacokinetics of sirolimus in patients with chronic hepatic impairment and in healthy adults: final report (protocol 468E1-134-US). Wyeth-Ayerst GMR-31056, 1997.

[52] Zimmerman JJ, Gurr JA, DiLea C. Study of the potential pharmacokinetic interaction between sirolimus (Rapamune) and microemulsion cyclosporine (Neoral) when administered concomitantly and four hours apart: final report (protocol 468E1-163-US). Wyeth-Ayerst GMR-31330, 1998.

[53] Zimmerman JJ, Miller MJ, DiLea C. Study of the potential pharmacokinetic interaction between a solid dose formulation of sirolimus (Rapamune) and microemulsion cyclosporine (Neoral) when administered concomitantly and four hours apart: final report (protocol 468H1-168-US). Wyeth-Ayerst GMR-31265, 1999.

[54] Knoll G, Selmani A, Zimmerman JJ, Gioud-Paquet M. A double-blind study in patients with severe psoriasis to assess the clinical activity and safety of rapamycin (sirolimus) alone or in association with a reduced dose of cyclosporine: final report. (protocol 0468E3-206-EU). Wyeth-Ayerst CSR-32070, 1998.

[55] Zimmerman JJ, Gurr JA, Burke JT. An open-label, single-dose, crossover, pharmacokinetic study of the potential interaction between sirolimus and diltiazem in healthy volunteers: final report (protocol 0468E1-135-EU). Wyeth-Ayerst GMR-33150, 1998.

[56] Zimmerman JJ, Gurr JA, DiLea C. Study of the potential pharmacokinetic interaction between sirolimus (Rapamune) and ketoconazole: final report (protocol 468E1-136-US). Wyeth-Ayerst GMR-31057, 1998.

[57] Zimmerman JJ, Gurr, JA, DiLea C. Study of the potential effect of rifampin on the pharmacokinetics of sirolimus (Rapamune) oral solution when administered concomitantly to healthy subjects: final report (protocol 0468E1-156-US). Wyeth-Ayerst GMR-31332, 1998.

[58] Fawl R, Guttman RM, Crouse W, Wade M, Chiang ST. A comparative study of the effect and equivalence of sirolimus oral liquid versus sirolimus tablets, administered concomitantly with cyclosporine and corticosteroids in renal allograft recipients: 6-month report (protocol 0468H1-309-GL). Wyeth-Ayerst GMR-34966, 1999.

[59] Huston EE, Qi K, Wade M, Singh A, Zimmerman JJ. A randomized, open-label, pilot study of cyclosporine elimination in renal allograft recipients treated with sirolimus, cyclosporine, and corticosteroids in the early postoperative period: 12-month interim report (protocol 0468E1-212-GL). Wyeth-Ayerst CSR-41764, 2001.

[60] DeLoskey RJ, Brault Y, Knoll G, Nègre E, Zimmerman JJ, Wang F. A randomized, open-label study of continuous therapy with cyclosporine and sirolimus versus induction with cyclosporine and sirolimus followed by continuous therapy with sirolimus in renal allograft recipients: 12-month interim report (protocol 0468H1-310-GL). Wyeth-Ayerst CSR-40858, 2001.

[61] Zimmerman JJ, Meloni FJ, Maida B. A randomized, double-blind, placebo-controlled study of the safety, tolerance, and preliminary pharmacokinetics of ascending multiple doses of orally administered sirolimus (rapamycin) in stable renal transplant recipients: final report (protocol 0468E1-112-GL). Wyeth-Ayerst GMR-26794, 1997.

[62] Rushworth DM. The validation of a routine HPLC/MS/MS assay to measure sirolimus in human whole blood (St. George's Hospital). Wyeth-Ayerst RPT-40162, 2000.

[63] Holt DW, Lee T, Johnston A. Measurement of sirolimus in whole blood using high-performance liquid chromatography with ultraviolet detection. *Clin Ther*. 2000; 22(Suppl B):38-48.

[64] Kramer WG, Chiang ST. Updated summary report of exploratory pharmacodynamic analysis of sirolimus based on pooled data of protocols 301-US and 302-GL. Wyeth-Ayerst GTR-37247, 1999.

[65] Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM. Chronic renal failure following liver transplantation. *Transplantation*. 1998;66:59-66.

[66] Gonwa TA. Hypertension and renal dysfunction in long-term liver transplant recipients. *Liver Transplantation*. 2001;7(Suppl 1):S22-S26.

[67] Myers BD, Ross J, Newton L, Luetscher J, Perlroth M. Cyclosporine-associated chronic nephropathy. *N Eng J Med*. 1984;311:699-705.

[68] Goldstein DJ, Zuech N, Sehgal V, Weinberg AD, Drusin R, Cohen D. Cyclosporine-associated end-stage nephropathy after cardiac transplantation. *Transplantation*. 1997;63:664-668.

11 TABLE OF STUDIES

TABLE OF STUDIES

Protocol No. (Location) Report No.	Study Design	Number in Study[a]
	1. PIVOTAL RMR STUDY (NON-IND)	
0468H1-310-GL (Non-IND)[b] (EU, AU, CA) CSR-40858	Phase 3, randomized, open-label study of continuous therapy with CsA and sirolimus versus induction with CsA and sirolimus followed by continuous therapy with sirolimus in renal allograft recipients.	525
	2. SUPPORTIVE RMR STUDY	
0468E1-212-GL (US, EU) CSR-41764	Phase 2, randomized, open-label, pilot study of CsA elimination in renal allograft recipients treated with sirolimus, CsA, and corticosteroids in the early postoperative period.	246
	3. SUPPORTIVE BASE THERAPY (SIROLIMUS VS CsA) STUDIES	
0468E1-207-EU (Non-IND)[b] CSR-37808	Phase 2, randomized, open, parallel-group study comparing sirolimus with CsA, each used in a triple-therapy regimen with corticosteroids and azathioprine, in the prevention of acute rejection episodes in renal allograft recipients.	83
0468E1-210-EU (Non-IND)[b] CSR-37804	Phase 2, randomized, open, parallel-group study comparing sirolimus with CsA, each used in a triple-therapy regimen with MMF and corticosteroids, for the prevention of acute rejection episodes in renal allograft recipients.	78

Country codes: EU = Europe, US = United States, CA = Canada, AU = Australia, GL = global.
Other abbreviations: CsA = cyclosporine, IND = Investigational New Drug, MMF = mycophenolate mofetil, RMR = Rapamune maintenance regimen.

a: As a patient could be withdrawn from the study at any point, the number of patients enrolled may not equal the total number of patients randomly assigned to treatment groups or the total number of patients receiving a dose of study drug.

b: This was a non-IND study that was planned for sites entirely outside the United States. These trials were carried out according to International Conference on Harmonisation and local regulatory guidelines.