CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021083

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21,083	**Submission Dates:** 12/15/98, 1/6/99, 5/21/99, 5/28/99, 6/4/99, 6/14/99, 7/9/99, 7/14/99
Generic Name, Strength and Formulation: Sirolimus (Rapamycin), 1 mg/mL oral solution	
Brand Name: Rapamune®	**Date Assigned:** 12/21/98
Applicant: Wyeth-Ayerst Research	**Final Review:** 8/11/99
Submission Code: 1P	**Reviewer:** Kofi A. Kumi, Ph.D.

Background

This review contains a summary of the studies that were reviewed from the studies submitted to Section 6 (Human Pharmacokinetics and Bioavailability) in support of NDA 21,083. Individual data and appendices are on file in the Division of Pharmaceutical Evaluation III.

The applicant is seeking approval of sirolimus 1 mg/mL oral solution for prophylaxis of organ rejection. Sirolimus is to be administered in a regimen with cyclosporine (CsA) and corticosteroids. The applicant is proposing a loading dose of 6 mg followed by a maintenance dose of 2mg per day. In high risk patients, the applicant is proposing a loading dose of 15 mg followed by a maintenance dose of 5 mg.

Sirolimus is a macrocyclic lactone similar to tacrolimus (FK 506) and CsA; however, it has unique immunosuppressive biochemical mechanism of action that is distinct from CsA and FK506. Sirolimus inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine interleukin (IL)-2, IL-4, IL-7 and IL-15. In cells, sirolimus binds to the immunophilin, FKBP-12, to generate an immunosuppressive complex. The FKBP-12 binds to and inhibits the activation of a kinase called mammalian target of rapamaycin (mTOR). Inhibition of mTOR by sirolimus suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle.

SYNOPSIS (EXPANDED)

Bioavailability/Food Effect: The bioavailability of sirolimus was determined using two stage population analysis method. One hundred and eighty subjects in 13 phase I study were given sirolimus as either single intravenous dose or single oral dose, or multiple oral doses. The bioavailability was estimated to be about 14%. It must be noted that the data used in the analysis were not from a crossover study but came from studies in which the

patient populations were different. Therefore, the computed bioavailability is an approximation of the absolute value.

High-fat meal (1.88 kcal; 54.7% fat) produced statistically significant changes in both the rate and extent of absorption of sirolimus. These changes were manifested as a 3.5-fold increase in t_{max}, a 34% decrease in C_{max}, and 35% increases in both AUC_t and AUC. The t ½ did not change with high fat meal. Systemic exposure to sirolimus was greater after administration with Tang (17% increase in AUC) than after administration with water. Peak concentration of sirolimus occurred sooner after administration with orange juice (decrease in t_{max} by 4 minutes) than administration with Tang (t_{max} increased by12 minutes) compared with after administration with water. Peak sirolimus concentrations were equivalent after administration with orange juice, Tang, or water. The applicant recommends orange juice and water may be used interchangeably as administration liquids for oral liquid sirolimus. The applicant's recommendation is acceptable.

Distribution/Protein Binding: Sirolimus is 92% bound to human plasma proteins. It binds mainly to serum albumin (97%), α1-acid glycoprotein and lipoproteins. Sirolimus partitions extensively into red blood cells. The Blood/Plasma ratio in stable renal transplant patients and healthy volunteers were 36.5 ± 17.9 and 79.9 ± 45.8, respectively.

Metabolism: In an open-label, nonrandomized design in which single oral doses of [^{14}C]-labeled sirolimus solution was administered to 6 healthy male subjects, the mean (range) total recovery of radioactivity from urine and feces after oral administration of [^{14}C] sirolimus was 93.2% (78.0% to 98.4%). Ninety-one percent of the radioactivity was recovered from feces and only 2.2% was excreted in urine. The excretion of total radioactivity in feces and urine was prolonged, and approximately 5 days were required for 90% recovery in individual subjects. Seven major metabolites were identified: several hydroxy (OH) sirolimus, hydroxy-demethyl sirolimus, dimethyl sirolimus,7-O-demethyl-sirolimus and 41-O-demethyl sirolimus. Sirolimus metabolites were not present as glucuronide or sulfate conjugates. The applicant reported that the metabolites have little or no immunologic activity and that the majority (> 90%) of the immunologic activity resides in the parent compound.

Based on a combination of correlation analysis, chemical inhibition, expressed human cytochrome P450 and enzyme induction, hepatic cytochrome P450 3A4 was identified as the major rapamycin drug metabolizing enzyme in human liver. Inhibitors of CYP3A4 (ketoconazole, nicardipine and cyclosporine) markedly inhibited sirolimus metabolism in incubations with human liver microsomes. Reports also indicate that sirolimus is a substrate for p-glycoprotein efflux transport system.

Pharmacokinetics

Single Dose/Dose Proportionality: In a parallel design, ascending, single oral dose study of sirolimus 0.3, 1.0, 5.0 and 8 mg/m^2 in health volunteers, the dose proportionality

of sirolimus pharmacokinetics were evaluated. The AUC and Cmax indicate there is no significant difference in the values when they are adjusted for dose; hence, increase in sirolimus concentrations were proportional to dose. Also, the clearance does not change with an increase in dose. The results indicate that, over the dose range of 1 to 8 mg/m^2, the pharmacokinetics of blood sirolimus was linear. However, there was large intersubject variability (CV > 30%) observed in this study. In a different incomplete block, cross-over design study, stable renal transplant patients received two out of three different doses of sirolimus 3, 6, and 12 mg/m^2. Estimates of Cmax and AUC were both shown to increase proportionally with dose; however, the confidence intervals were large and the intersubject variabilities for C_{max} and AUC were also large (>30%).

Pharmacokinetics in Patients: The pharmacokinetics was investigated in a subset of patients in the pivotal clinical trial. In this study, sirolimus was administered with cyclosporine (Neoral® administered 4 hours apart) and corticosteroids. Group A patients received sirolimus 5 mg (loading dose of 15 mg), Group B received sirolimus 2 mg (loading dose 6 mg) and Group C received azathioprine 2-3 mg/kg (loading dose of 5 mg/kg). Blood samples for the determination of sirolimus and cyclosporine pharmacokinetic profiles were taken at the end of 1, 3 and 6 month after daily administration of the dosing regimen. Whole blood sirolimus concentrations were not significantly different over the dose interval at any time-point with respect to either treatment or month. There were no statistically significant differences for any of the pharmacokinetic parameters with respect to either treatment group or month or race. However, there was a trend of blacks having lower clearances of sirolimus compared to non-blacks. Mean Cl/F/Wt values for black patients were decreased 22.8% and 37.6% compared to non-black patients in the 2 and 5mg sirolimus dose groups, respectively. Therefore even though the differences were not statistically significant, black patients on the average tended to have higher exposures than non-black patients (figures on the following pages). The following table contains the combined pharmacokinetic parameters for sirolimus.

Table 1 WHOLE BLOOD SIROLIMUS PHARMACOKINETIC PARAMETERS IN POST-TRANSPLANT PATIENTS

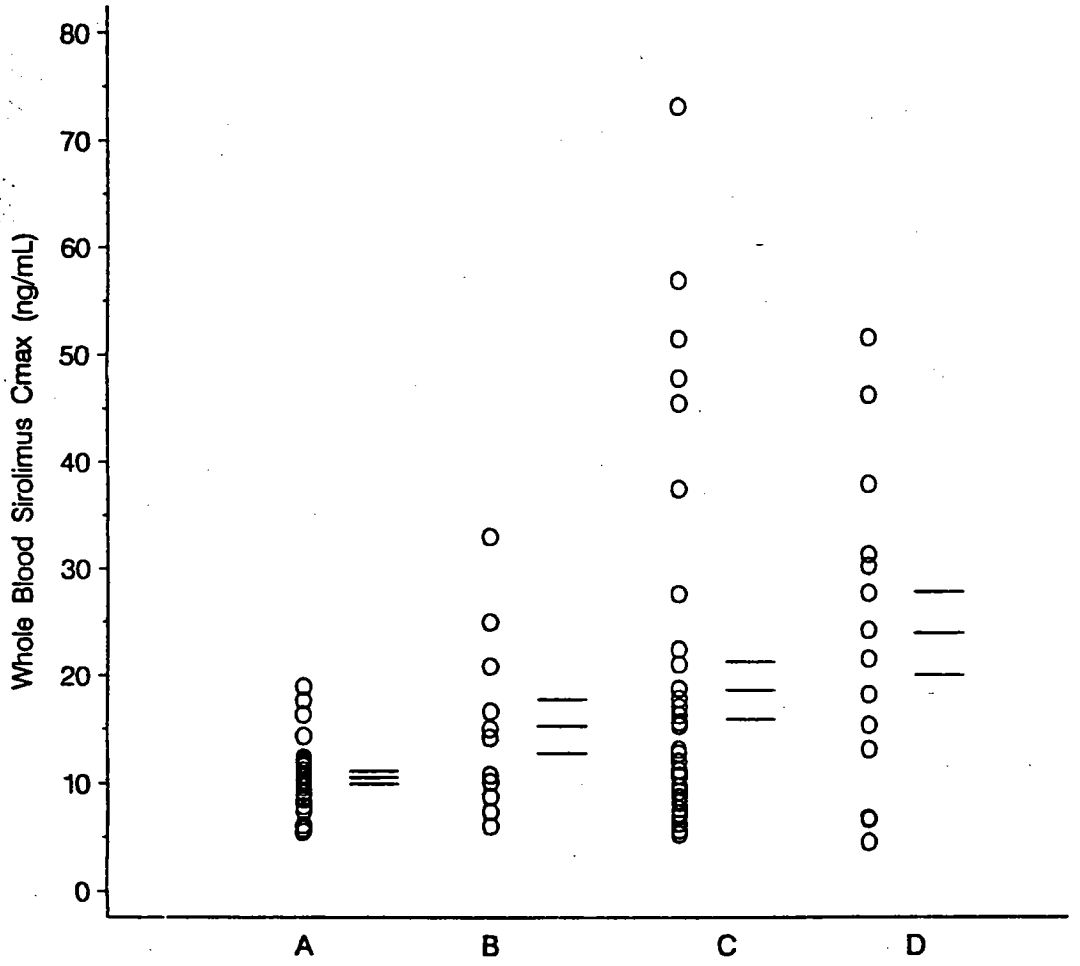
Treatment	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$ (ng•h/mL)	CL/F/WT (mL/h/kg)
2-mg sirolimus (n = 19)	12.2 ± 6.2[a,b] (51.1/23.2)	3.01 ± 2.40 (79.6/45.5)	158 ± 70 (44.1/23.5)	182 ± 72 (39.7/20.3)
5-mg sirolimus (n = 23)	37.4 ± 21 (56.2/43.6)	1.84 ± 1.30 (70.4/46.3)	396 ± 193 (48.7/40.8)	221 ± 143 (64.7/31.6)
Source of Variability			p-values from ANOVA[c]	
Treatment	0.14	0.14	0.38	0.27
Race	0.17	0.41	0.13	0.12
Month	0.50	0.98	0.42	0.74

a: Data presented as the mean ± SD (intersubject/intrasubject %CVs).
b: The overall averages among subjects include the average value in each patient over time.
c: $C_{max,ss}$ and $AUC_{\tau,ss}$ were normalized to a 2-mg dose prior to ANOVA.

The following table provides the whole blood sirolimus trough concentrations. Dose normalized whole blood sirolimus trough concentrations were significantly different.

Figure 1

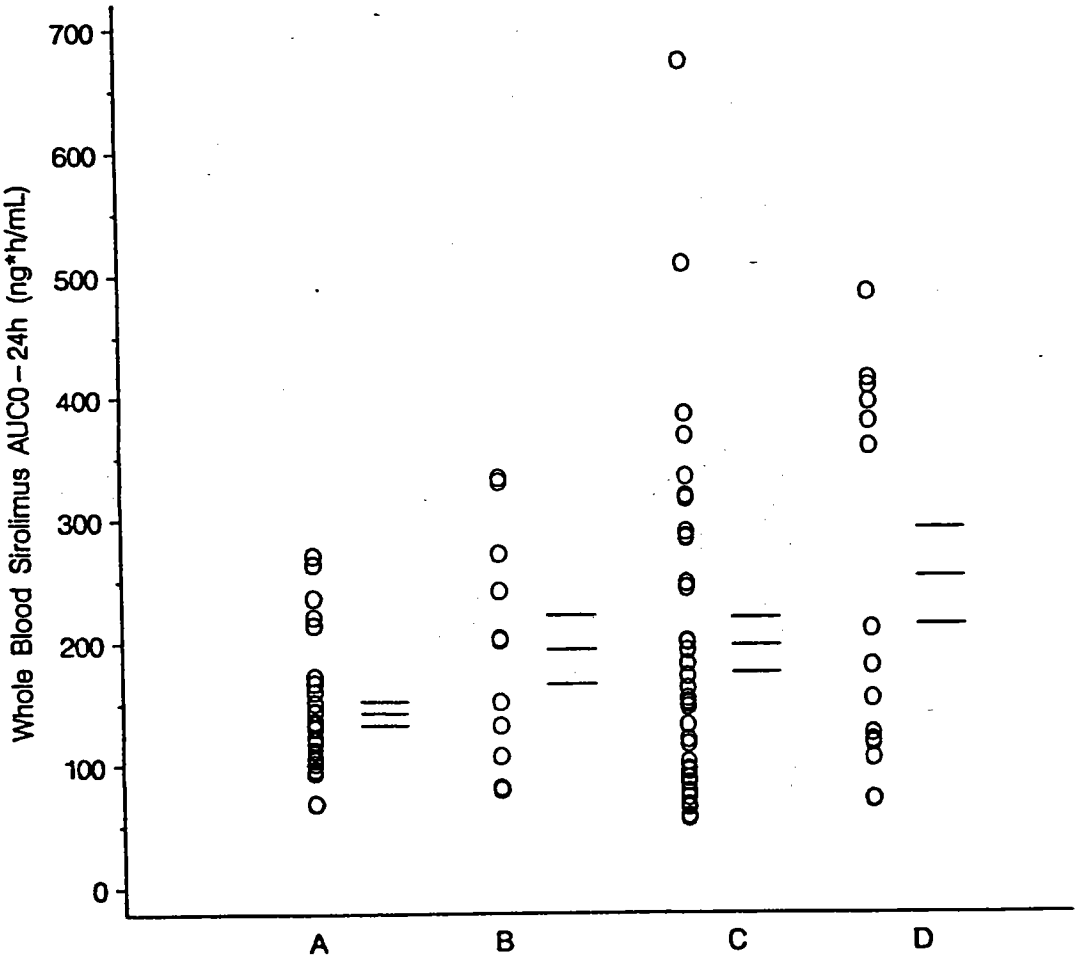
Comparison of Whole Blood Sirolimus Cmax
(Normalized to 2 mg Dose) in Individual Patients
Among Blacks and Nonblacks and Assigned Sirolimus Dose Groups
Protocol 0468E1–301–US



— Mean +/– SE
A = 2 mg (Nonblack), B = 2 mg (Black)
C = 5 mg (Nonblack), D = 5 mg (Black)

Figure 2

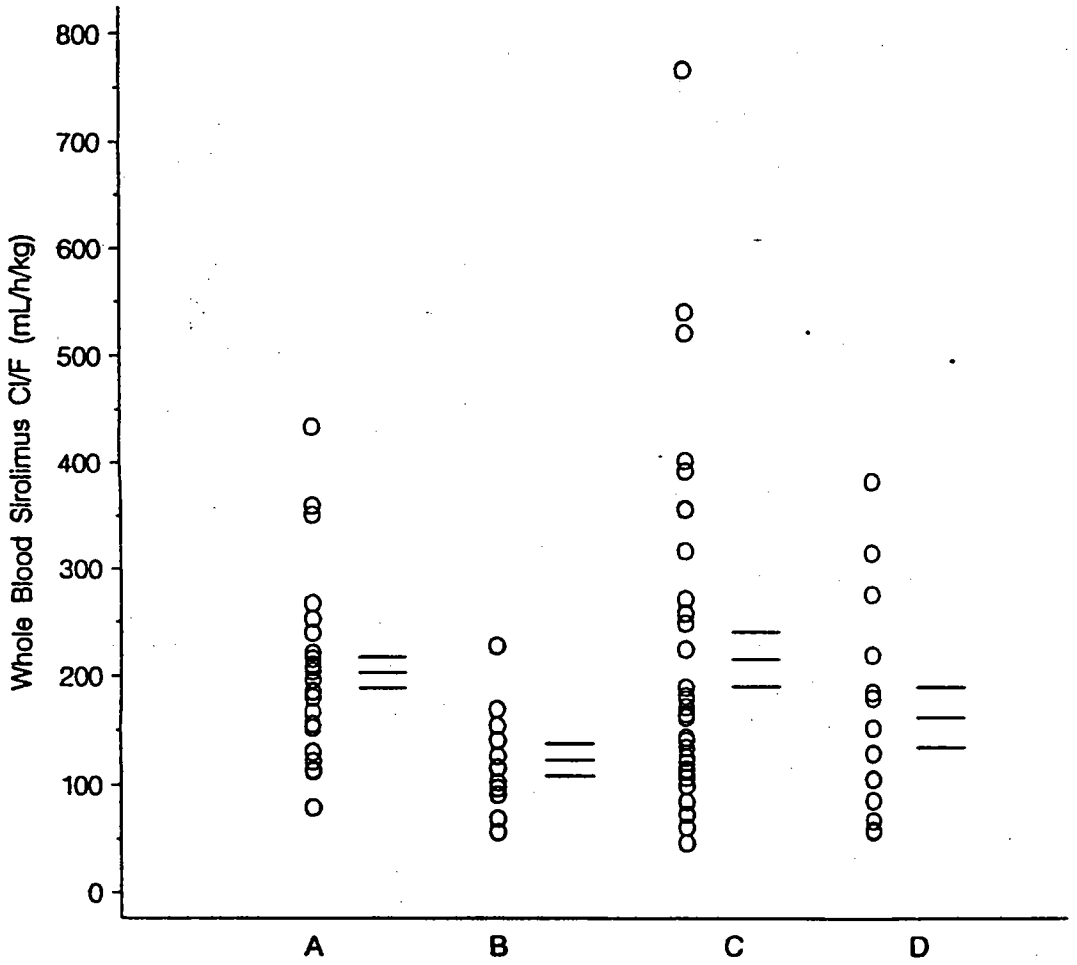
Comparison of Whole Blood Sirolimus AUC
(Normalized to 2 mg Dose) in Individual Patients
Among Blacks and Nonblacks and Assigned Sirolimus Dose Groups
Protocol 0468E1-301-US



___ Mean +/- SE
A = 2 mg (Nonblack), B = 2 mg (Black)
C = 5 mg (Nonblack), D = 5 mg (Black)

Figure 3

Comparison of Whole Blood Sirolimus CL/F
in Individual Patients
Among Blacks and Nonblacks and Assigned Sirolimus Dose Groups
Protocol 0468E1-301-US



___ Mean +/- SE
A = 2 mg (Nonblack), B = 2 mg (Black)
C = 5 mg (Nonblack), D = 5 mg (Black)

There was no significant difference in the pharmacokinetics between black and non-black patients. There was large intra-individual variability in the trough concentrations.

Table 2 AVERAGE TROUGH WHOLE BLOOD SIROLIMUS CONCENTRATIONS OVER TIME IN RENAL ALLOGRAFT RECIPIENTS

Treatment	Race	n	Trough[a,b] (ng/mL)	C.V. (%) Interindividual	C.V. (%) Intraindividual
2-mg sirolimus	Non-black	179	8.58 ± 3.98	46.4	37.8
	Black	47	8.62 ± 4.13	47.9	34.6
	Combined	226	8.59 ± 4.01	46.6	37.1
5-mg sirolimus	Non-black	170	17.1 ± 7.45	43.5	38.6
	Black	49	17.7 ± 7.05	39.8	39.3
	Combined	219	17.3 ± 7.35	42.6	38.8

Source of Variation	P-value from ANOVA[c]
Treatment	0.050
Race	0.38
Treat*Race	0.39

a: Trough concentrations presented as mean ± SD
b: Mean of average troughs (by area method) across days in individual patients
c: Individual trough concentrations were normalized to 2 mg prior to ANOVA

There were no statistically significant differences in whole blood CsA pharmacokinetic parameters with respect to period (months 1, 3, and 6). A statistically significant effect for treatment was observed in dose-normalized $AUC_{\tau,ss}$ and CL/F/WT. A statistically significant difference between black patients and non-black patients was observed only for whole blood CsA CL/F/WT. The CL/F/WT values for black patients in the 2-mg, 5-mg sirolimus and sirolimus placebo treatment groups were decreased 33.7%, 9.4% and 16.9% compared to non-black patients. The variability in clearance values was large ranging from 6.2% to 50.7% in blacks and 5.7% to 56.6% in non-blacks (see figures on the following pages). Generally, there were no significant differences in the actual trough CsA concentrations; CsA trough concentrations were per protocol maintained within pre-specified ranges. The trough CsA concentrations remained at steady state over 1 to 6 months for all treatment groups. It must noted that it was observed that in most patients in the pivotal clinical trials, the average CsA trough concentrations tended to be at the upper end of the target CsA concentration range. The medical officers on the review team were aware of this observation. The clinical implications of the observation that the average trough CsA concentrations in the pivotal study tended to be at the upper end the target range is not clear.

Table 3 WHOLE BLOOD CYCLOSPORINE PHARMACOKINETIC PARAMETERS IN POST-TRANSPLANT PATIENTS

Treatment	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$ (ng•h/mL)	CL/F/WT (mL/h/kg)
2-mg sirolimus (n = 19)	1337 ± 368[a,b] (27.5/33.2)	1.85 ± 0.66 (35.8/31.4)	7058 ± 1698 (24.1/28.9)	397 ± 181 (45.5/25.5)
5-mg sirolimus (n = 24)	1414 ± 460 (32.5/36.7)	2.02 ± 0.78 (38.8/46.2)	6859 ± 1840 (26.8/34.8)	340 ± 80 (23.4/25.3)
Placebo (n = 13)	1269 ± 260 (20.5/35.4)	1.93 ± 0.78 (40.3/40.7)	6056 ± 1067 (17.6/24.4)	566 ± 194 (34.2/26.0)
Source of Variability	p-values from ANOVA[c]			
Treatment	0.06	0.65	0.008	0.003
Race	0.67	0.51	0.56	0.05
Month	0.13	0.41	0.44	0.47

a: Data presented as the mean ± SD (intersubject/intrasubject %CVs).
b: The overall averages among subjects include the average value in each patient over time.
c: $C_{max,ss}$ and $AUC_{\tau,ss}$ were normalized to a 100-mg dose prior to ANOVA.

Table 4 AVERAGE TROUGH WHOLE BLOOD CYCLOSPORINE CONCENTRATIONS OVER TIME IN RENAL ALLOGRAFT RECIPIENTS[a]

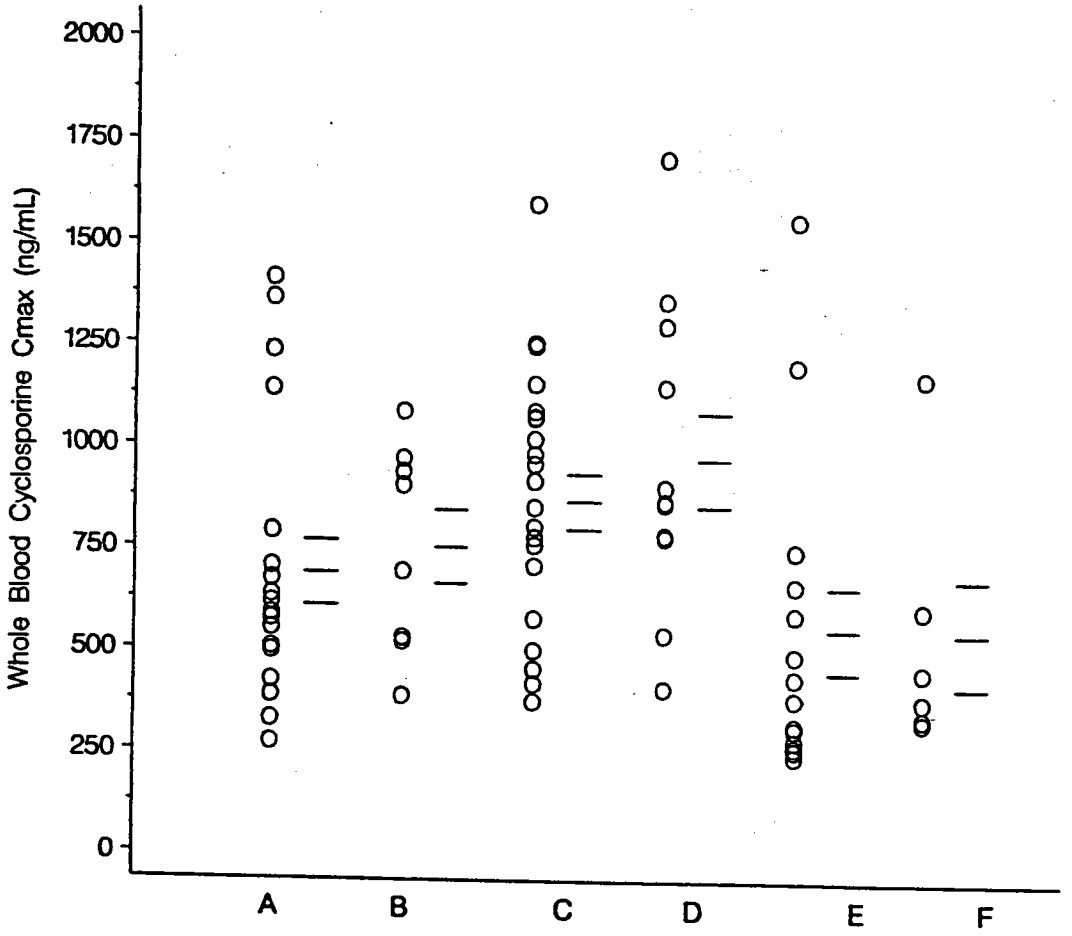
Treatment	Race	Month 1 n	Month 1 ng/mL (%CV)	Months 2 - 3 n	Months 2 - 3 ng/mL (%CV)	Months 4 - 6 n	Months 4 - 6 ng/mL (%CV)
2-mg Sirolimus	Non-black	81	361 (41.7/31.2)	117	317 (45.4/26.5)	145	267 (33.7/28.6)
	Black	19	367 (37.0/37.5)	29	324 (37.8/33.8)	29	268 (35.2/32.1)
	Overall	100	363 (40.7/32.4)	146	319 (43.8/27.9)	174	268 (33.8/29.2)
5-mg Sirolimus	Non-black	69	350 (53.3/30.9)	93	302 (33.6/26.3)	128	247 (34.6/23.6)
	Black	23	403 (46.5/40.0)	33	287 (38.4/27.5)	37	259 (31.5/27.4)
	Overall	92	363 (51.5/33.2)	126	298 (34.8/26.7)	165	250 (33.8/24.5)
Placebo	Non-black	51	358 (36.4/33.9)	43	314 (24.0/24.7)	59	253 (25.3/17.2)
	Black	17	438 (56.0/36.3)	20	292 (23.7/25.4)	22	278 (27.5/22.1)
	Overall	68	378 (44.4/34.5	63	307 (24.0/24.9)	81	260 (26.2/18.6)

Trough Concentration	Source of Variation	p-value from ANOVA
Actual	Treatment	0.67
	Race	0.72
	Interval	0.001
Normalized[b]	Treatment	0.02
	Race	0.03
	Interval	0.001

a: Mean of average troughs (by area method) across days in individual patients.
b: Individual trough concentrations were normalized to 100 mg prior to ANOVA.

Figure 4

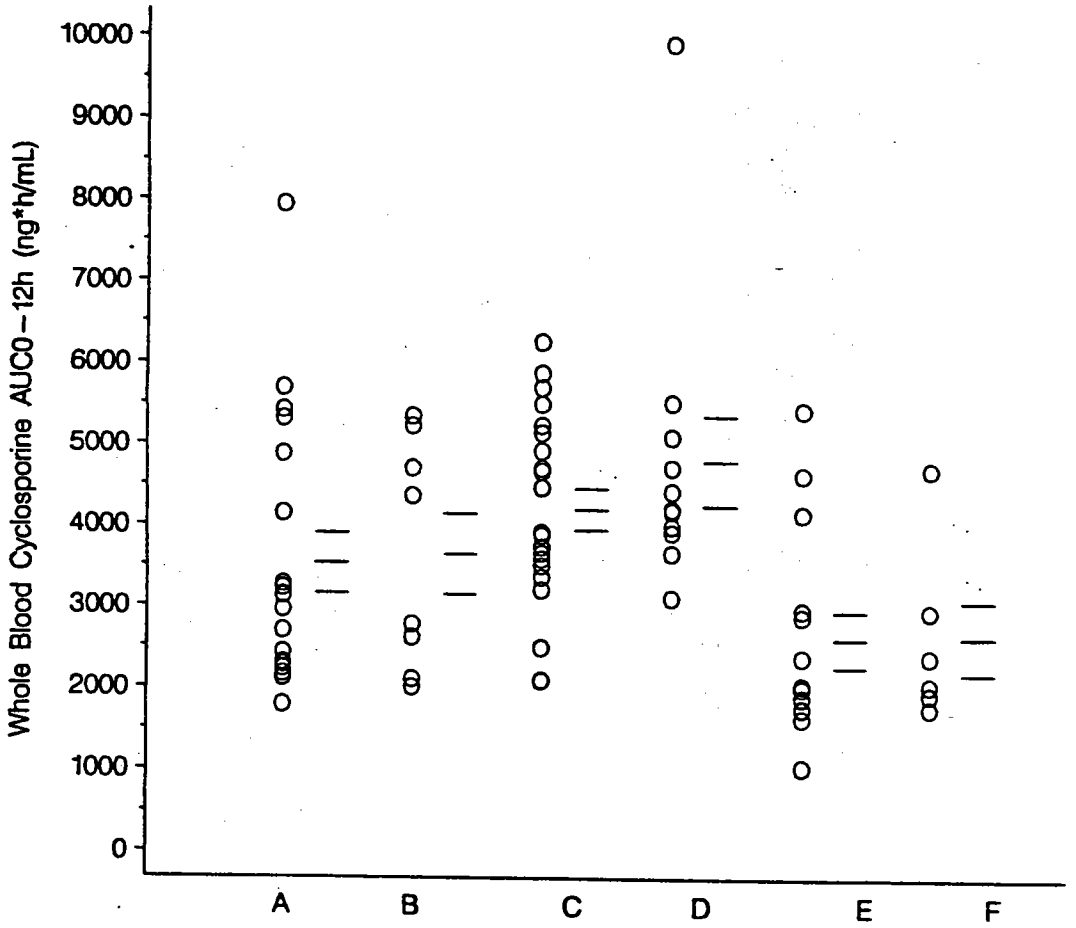
Comparison of Whole Blood Cyclosporine Cmax
(Normalized to 100 mg Dose) in Individual Patients
Among Blacks and Nonblacks and Assigned Sirolimus Dose Groups
Protocol 0468E1-301-US



___ Mean +/- SE
A = 2 mg (Nonblack), B = 2 mg (Black)
C = 5 mg (Nonblack), D = 5 mg (Black)
E = Placebo (Nonblack), F = Placebo (Black)

Figure 5

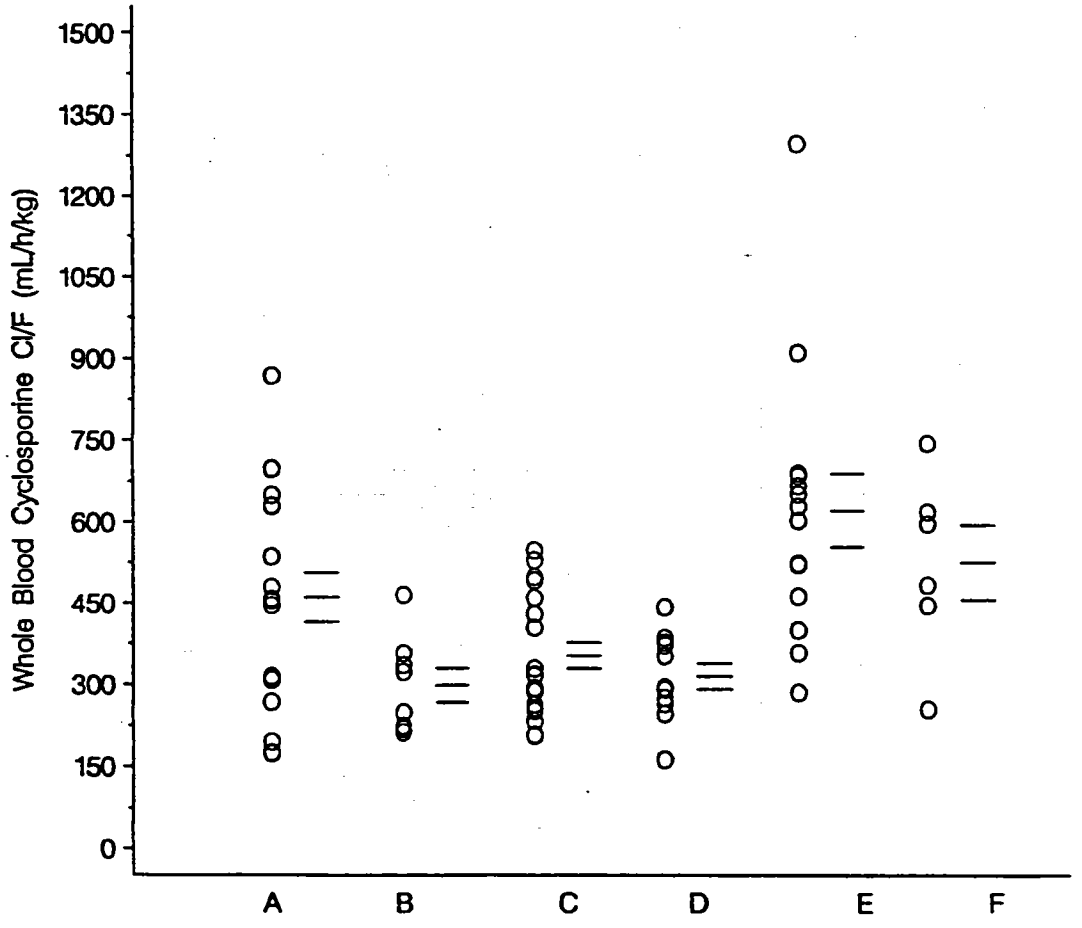
Comparison of Whole Blood Cyclosporine AUC
(Normalized to 100 mg Dose) in Individual Patients
Among Blacks and Nonblacks and Assigned Sirolimus Dose Groups
Protocol 0468E1-301-US



___ Mean +/- SE
A = 2 mg (Nonblack), B = 2 mg (Black)
C = 5 mg (Nonblack), D = 5 mg (Black)
E = Placebo (Nonblack), F = Placebo (Black)

Figure 6

Comparison of Whole Blood Cyclosporine Cl/F
in Individual Patients
Among Blacks and Nonblacks and Assigned Sirolimus Dose Groups
Protocol 0468E1-301-US



___ Mean +/- SE
A = 2 mg (Nonblack), B = 2 mg (Black)
C = 5 mg (Nonblack), D = 5 mg (Black)
E = Placebo (Nonblack), F = Placebo (Black)

Pharmacokinetic-Pharmacodynamic (PK/PD) Evaluation

The influence of sirolimus and cyclosporine concentrations on acute rejection, confirmed by biopsy, was evaluated using logistic regression. Also, an evaluation of the relationship between trough concentrations and laboratory parameter changes was conducted.

Average sirolimus and CsA trough concentrations were calculated using the area under the curve of trough concentrations over the first 75 days of treatment. Average trough sirolimus concentrations were higher in patients who did not exhibit allograft rejections than in patients who did although the variability in average trough concentrations across patients was high (CV: 60% for non-rejectors and 90% for rejectors). Mean CsA average trough concentrations were also higher in patients that did not reject than in patients that did, although as observed for sirolimus, the variability was high (CV: 40% and 53% for rejectors and non-rejectors, respectively). The data suggested that there were no significant differences among gender, race and donor with respect to acute rejections during the first two months.

A higher number of HLA mismatches was also significantly associated with increased incidence of allograft rejection. Donor's age, race, sex, donor status or ischemia time appeared not to be a significant predictor of acute rejection. Patients having average sirolimus concentration less than 3.50 ng/mL had a significant increase risk of acute rejection. Similarly, patients having an average CsA trough concentrations less than 260.4 ng/mL were more likely to have an acute rejection. Sirolimus, when co-administered, with CsA is predicted to be effective than CsA alone in reducing the probability of rejection rate. Increase in sirolimus concentration results in a reduction in the probability of rejection. A reduction in CsA concentration does not appear to have a pronounced effect on the probability of rejection.

The logistic regression analysis suggests that there was a significant relationship between the probability of acute rejection during the first 75 days and average trough concentrations of sirolimus and CsA and HLA mismatch scores. An increase in sirolimus and CsA trough concentrations predict a significant reduction of the probability of allograft rejection. The pharmacodynamic (PD)-efficacy response curve for cyclosporine suggests that it is not necessary to keep cyclosporine average trough concentrations as high as was suggested for maintenance therapy (200 – 350 ng/mL) in order for the combined therapy to be effective if the sirolimus concentration is maintained between 15 – 25 ng/mL (figures and tables on following pages). On the other hand, the combined therapy is also predicted to be effective even if the sirolimus concentration is about 10 ng/mL as long as the CsA concentration is maintained at about 350 ng/mL.

Changes from baseline in platelet counts decreased with increased drug exposure, age and duration in the study. Hemoglobin values increased with increase exposure to sirolimus and cyclosporine (CsA). White blood cell counts (WBC) appeared to be independent of study drug exposure. Significant increases from baseline in fasting cholesterol were associated with sirolimus and CsA exposure. Triglyceride changes were

Figure 7. Probability of Acute Rejection vs Sirolimus Concentrations
At Various Cyclosporine Concentrations

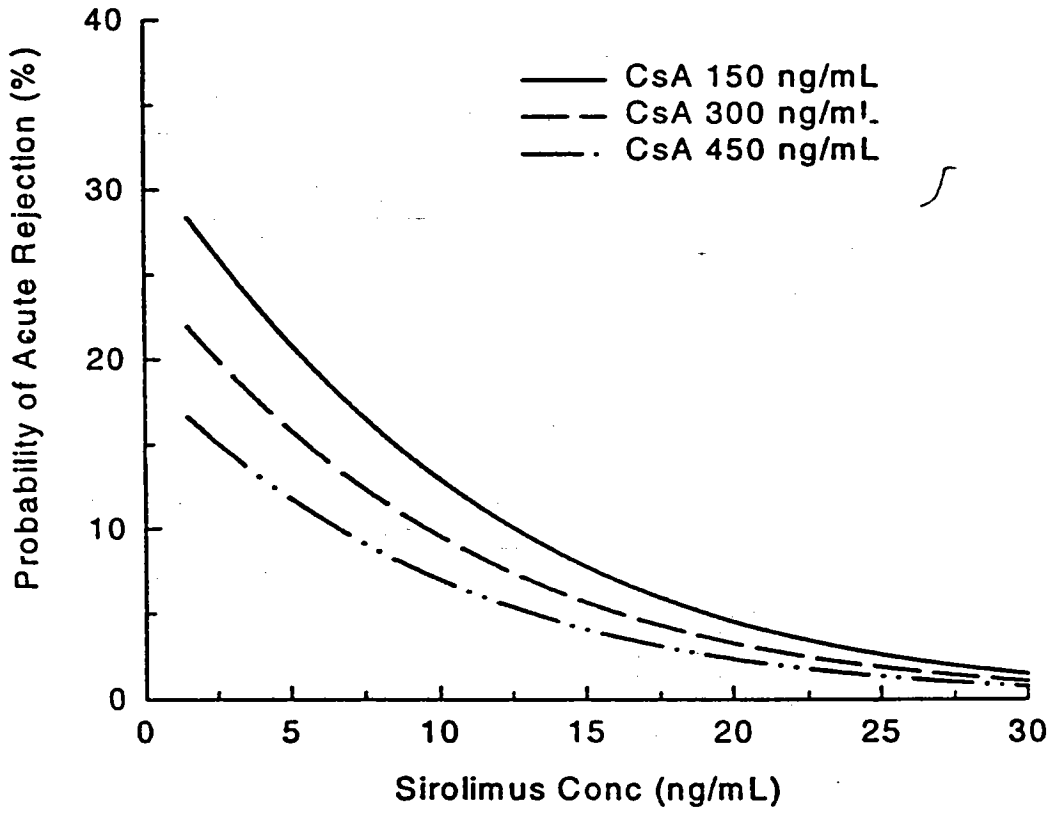


Figure 8

Figure 8 - Probability of Acute Rejection vs. Cyclosporine Concentrations At Various Sirolimus Concentrations

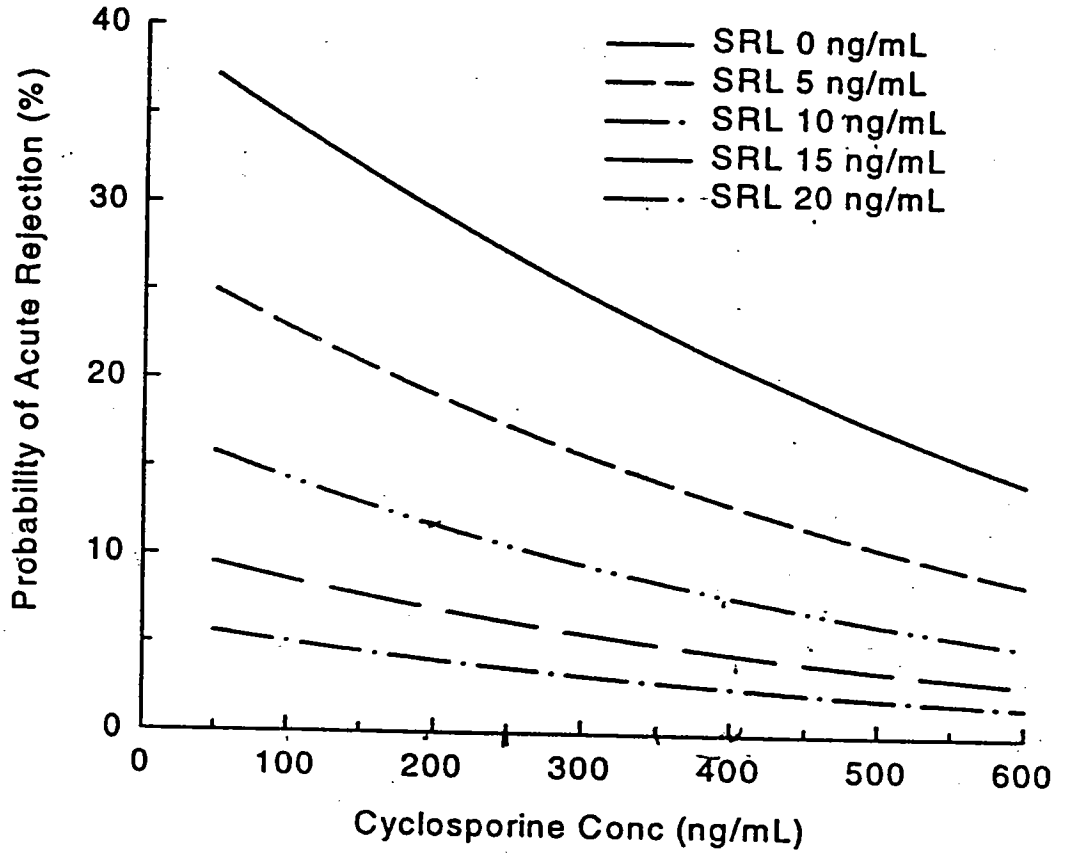


Table 5 - DESCRIPTIVE STATISTICS OF DRUG EXPOSURES AND DEMOGRAPHIC VARIABLES IN RENAL TRANSPLANT RECIPIENTS RECEIVING ADMINISTRATION OF SIROLIMUS (OR PLACEBO OR AZATHIOPRINE), CsA, AND STEROIDS BY PATIENT'S REJECTION STATUS DURING MONTHS 1 AND 2 (DAY≤75)

(ALL TREATMENT GROUPS)

PROTOCOLS 0468E1-301-US AND 0468E1-302-GL

	TREATMENT GROUP	PATIENTS WITH NO REJECTIONS				PATIENTS WITH REJECTIONS				T-TEST P-VALUE
		N	MEAN	SD	CV%	N	MEAN	SD	CV%	
AVERAGE SIROLIMUS TROUGH	SIROLIMUS	789	12.83	7.68	59.9	132	8.68	7.78	89.6	<0.001**
	CONTROL	176	0	0	-	95	0	0	-	-
	OVERALL	965	10.49	8.53	81.3	227	5.05	7.31	144.9	<0.001**
AVERAGE CsA TROUGH	SIROLIMUS	745	349.77	141.07	40.3	68	280.41	138.04	49.2	<0.001**
	CONTROL	168	330.53	127.13	38.5	58	328.21	181.21	55.2	0.928
	OVERALL	913	346.23	138.74	40.1	126	302.42	160.50	53.1	0.004**
RECIPIENT AGE	SIROLIMUS	812	45.39	12.91	28.4	137	45.36	12.33	27.2	0.984
	CONTROL	179	46.70	12.63	27.0	97	43.61	13.50	30.9	0.059
	OVERALL	991	45.63	12.87	28.2	234	44.64	12.83	28.7	0.290
HLA MISMATCH	SIROLIMUS	807	3.39	1.58	46.6	137	3.98	1.44	36.3	<0.001**
	CONTROL	179	3.19	1.62	50.7	97	3.77	1.32	35.0	0.001**
	OVERALL	986	3.35	1.59	47.4	234	3.89	1.39	35.8	<0.001**
ISCHEMIA TIME	SIROLIMUS	809	13.13	10.22	77.8	137	14.34	9.28	64.7	0.194
	CONTROL	178	15.16	9.57	63.1	97	13.01	10.29	79.1	0.083
	OVERALL	987	13.50	10.13	75.1	234	13.79	9.71	70.4	0.690
DONOR AGE	SIROLIMUS	811	38.02	15.53	40.9	136	40.85	15.88	38.9	0.050
	CONTROL	179	36.69	16.14	44.0	97	36.31	15.19	41.8	0.848
	OVERALL	990	37.78	15.65	41.4	233	38.96	15.72	40.4	0.300

* P<0.050
** P<0.010
NOTE: THE NUMBER OF HLA MISMATCHES WAS TREATED AS A CONTINUOUS VARIABLE IN ALL STATISTICAL SUMMARIZATIONS AND ANALYSES

Table 6 - RESULTS OF QUARTILE ANALYSES EXAMINING THE LINEARITY OF THE LOGIT OF THE MAIN UNIVARIATE MODEL SELECTED BY STEPWISE REGRESSION WITH RESPECT TO THE INCIDENCE OF ACUTE REJECTION DURING MONTHS 1 AND 2 (DAY≤75) IN RENAL TRANSPLANT RECIPIENTS RECEIVING ADMINISTRATION OF SIROLIMUS (OR PLACEBO OR AZATHIOPRINE), CsA, AND STEROIDS (ALL TREATMENT GROUPS)

PROTOCOLS 0468E1-301-US AND 0468E1-302-GL

INDEPENDENT VARIABLE	STATISTIC	QUARTILE 1	2	3	4
AVERAGE SIROLIMUS TROUGH (ng/mL)	QUARTILE RANGE	0 – 3.50	3.51 – 8.28	8.29 – 14.25	>14.25
	N	257	256	257	256
	MEAN	0.27	6.23	11.07	20.85
	MEDIAN	0	6.50	10.84	19.23
	ESTIMATED SLOPE		-1.2575	-1.7998	-1.9636
	ODDS RATIO		0.284	0.165	0.140
	95% CI		(0.171, 0.462)	(0.089, 0.291)	(0.071, 0.257)
AVERAGE CsA TROUGH (ng/mL)	QUARTILE RANGE	20.83 – 260.39	260.40 – 326.88	326.89 – 400.66	>400.66
	N	257	256	257	256
	MEAN	201.65	292.00	362.76	513.14
	MEDIAN	211.41	290.41	361.94	466.10
	ESTIMATED SLOPE		-1.2965	-1.0138	-0.7641
	ODDS RATIO		0.273	0.363	0.466
	95% CI		(0.152, 0.474)	(0.206, 0.621)	(0.273, 0.778)
HLA MISMATCH	QUARTILE RANGE	0 – 2	3	4 – 5	>5
	N	261	284	381	100
	MEAN	1.36	3	4.47	6
	MEDIAN	2	3	4	6
	ESTIMATED SLOPE		0.4890	0.8433	1.5058
	ODDS RATIO		1.631	2.324	4.508
	95% CI		(0.890, 3.059)	(1.344, 4.177)	(2.223, 9.232)

NOTE: THE BOX-TIDWELL COEFFICIENT WAS SIGNIFICANT FOR AVERAGE TROUGH SIROLIMUS (P = 0.010) AND FOR AVERAGE TROUGH CsA (P < 0.001) BUT NOT FOR NUMBER OF HLA MISMATCHES (P = 0.705).

NOTE: FALSE POSITIVE SIROLIMUS CONCENTRATIONS FOR PATIENTS IN THE CONTROL (PLACEBO OR AZATHIOPRINE) TREATMENT WERE SET TO ZERO.

NOTE: THE NUMBER OF HLA MISMATCHES WAS TREATED AS A CONTINUOUS VARIABLE IN ALL STATISTICAL SUMMARIZATIONS AND ANALYSES.

found to be positively associated with sirolimus and CsA exposure. Reduction in glomerular filtration rate (GFR) was observed with increased concentrations indicating a negative relationship between GFR and sirolimus and CSA exposure.

The PD modeling suggests that in the presence of sirolimus, CsA concentrations can be lower than the usual targets while maintaining adequate protection from acute rejection. The results of the PK/PD modeling exercise predicts the likely therapeutic range of sirolimus to be between 3.5 to 30 ng/mL based on the logistic regression models for laboratory values and the probability of acute rejection as related to sirolimus trough concentrations. However, based on the logistic regression modeling exercise considering both efficacy and safety, the optimum therapeutic range is likely between 8.3 to 25 ng/mL. The pivotal clinical studies were conducted without the benefit of therapeutic drug monitoring (TDM). A rational approach that the applicant should consider for future studies is that the applicant employs TDM to validate the predicted optimum trough concentration range in an effort to optimize the dosing regimen for sirolimus in renal transplant patients. Also, the applicant should continue to evaluate whether lower CsA concentrations in combination with sirolimus is efficacious and has an acceptable or better safety profile.

Pharmacokinetics in Special Populations:

Hepatic Impairment Patients (Pugh Classifications A and B)

A significant decrease in sirolimus clearance (CL/F) and AUC was computed when the hepatically impaired group was compared to the healthy patients; however, Cmax was not significantly different. AUC was 61% higher and Cl/F/Wt values were 33% lower when the hepatic impaired patients were compared to healthy patients; Cmax was not significantly different between the two groups. It is recommended that sirolimus concentrations be reduced by about 30% and caution should be exercised if sirolimus is to be administered to hepatically impaired patients. The effect of severe hepatic impairments on the pharmacokinetics of sirolimus is not known and it is recommended that caution should be exercised if it is at all necessary to use sirolimus in these patients.

Popula-tion	Cmax (ng/mL)	Tmax (hr)	T ½ (hr)	AUC (ng*h/ mL)	Cl/F/Kg (mL/hr/ kg	Vss/F L/kg	MRT (hr)
Hepatic	77.9 ± 23.1	0.84 ± 0.17	112.5 ± 40.5*	1566.7 ± 616*	144 ± 62*	17.5 ± 6.2	135.4 ± 56*
Health	78.2 ± 18.3	0.82 ± 0.17	78.9 ± 12.1	970.1 ± 272	215 ± 76	17.4 ± 5.9	82.4 ± 13.2

*significant at $P < 0.05$

Pharmacokinetics in Pediatric Dialysis Patients

The pharmacokinetics of sirolimus in pediatric patients with stable chronic renal failure was assessed. The terminal disposition half-life (t ½) of sirolimus in blood was long, as reflected by the mean (range) values of 75.6 (33.5 to 166) hours in children 5 – 11 years old and 57.4 (40.4 to 95.9) hours in children 12 – 18 years of age. The weight-normalized apparent oral clearance (CL/F) for whole blood sirolimus showed significant differences with respect to both dose and age. The intersubject variability in CL/F values were great; the %CV values of 77% in pediatric patients aged 5 –11 years and 51.7% in pediatric patients aged 12 – 18 years. There were no significant differences in either MRT or Vss/F among age and dose groups. The following table provides across study comparison of the results from this study and that of healthy adults

Table 8 A COMPARISON OF SIROLIMUS PHARMACOKINETIC PARAMETERS AMONG PEDIATRIC DIALYSIS PATIENTS AND HEALTHY ADULTS

	Pediatric Dialysis Patients (Sirolimus Dose: 1, 3, and 9 mg/m²) (5 - 11 y)		(12 - 18 y)		Healthy Adults (Sirolimus Dose: 1, 3, 5, and 8 mg/m²) 19 - 36 years		ANOVA p-value (Tukey's comparison)[a]
Parameter	n	Mean ± SD (range)	n	Mean ± SD (range)	n	Mean ± SD (range)	
Age (y)	7	7.6 ± 2.4 (5 - 11)	9	15.2 ± 1.3 (14 - 17)	25	26.1 ± 5.2 (19 - 36)	-
t_{max} (h)	7	1.05 ± 0.45 (0.67 - 2.0)	9	0.82 ± 0.17 (0.67 - 1.0)	25	0.72 ± 0.21 (0.33 - 1.0)	0.021 (A > C)
$t_{1/2}$ (h)	7	75.6 ± 43.1 (33.5 - 166)	7	57.4 ± 19.1 (40.4 - 95.9)	25	80.7 ± 15.4 (55.7 - 113)	0.097
CL/F/WT (mL/h/kg)	7	544 ± 463 (221 - 1551)	7	443 ± 268 (182 - 900)	25	287 ± 111 (145 - 567)	0.037 (A > C)
V_{ss}/F/WT (L/kg)	7	30.5 ± 16.7 (14.4 - 59.4)	7	25.3 ± 15.2 (8.5 - 44.9)	25	23.4 ± 9.6 (9.8 - 51.3)	0.41
B/P	3	24.2 ± 10.8 (12.4 - 33.4)	5	29.7 ± 12.6 (13.8 - 45.4)	25	35.6 ± 11.7 (15.0 - 67.1)	0.22

a: A = Pediatric (5 - 11 y); B = Pediatric (12 - 18 y); C = Healthy Adults (19 - 36 y)

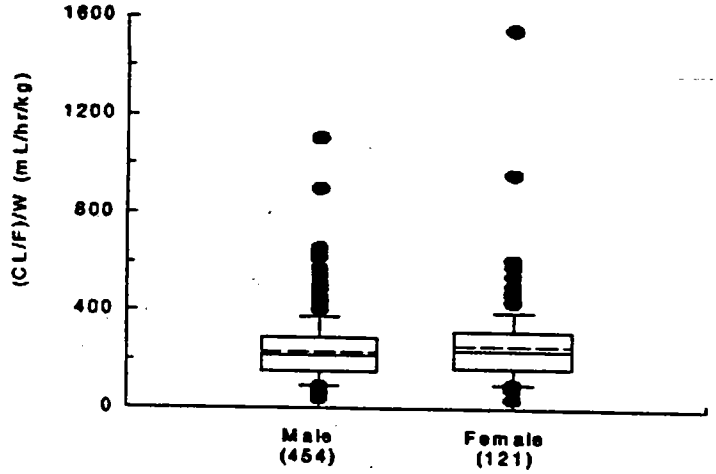
Statistically significant differences were observed in tmax and Cl/F/Wt. The tmax was longer (about 20 mins) in the 5 – 11 year olds compared to healthy adults. Cl/F/Wt of the 5 – 11 year old was increased by about 90% compared to healthy adults. When compared to the values of the subset of patients in the pivotal clinical study, the mean Cl/F/Wt of the 5 –11 year old was increased by approximately 115%.

Gender: The effect of gender on sirolimus pharmacokinetic parameters was studied using a two stage population analysis. This method revealed a statistically significant effect of gender on t ½ and Cl/F/Wt. The difference in t ½ and Cl/F/Wt were 15 and 12%, respectively. As indicated in the box plot on the following page, the data for the analysis

were obtained from 454 males compared to only 121 females. The %CV in Cl/F/Wt for males and females were 53.1 and 67.7, respectively. The differences in clearance were small and should be interpreted with caution because of the relatively few female patients and the variability in the data. The significance of the noted differences, if any, could not be ascertained from this analysis.

Figure 9

1. BOX-AND-WHISKER PLOT OF CL/F/WT BY GENDER



Drug Interactions

Sirolimus is reported to be a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein (P-gp), therefore, most of the investigations were concerned with delineating the effect between sirolimus and drugs that also interact with CYP3A4 and P-gp.

Diltiazem: Single doses of diltiazem (120 mg) alone, sirolimus (10 mg) alone, and the two drugs concomitantly were administered to 18 healthy adults in a randomized, 3-period, crossover study. Administration of a single dose of diltiazem (120 mg) affected both the rate and extent of absorption of sirolimus. The geometric least-squares (GLS) mean ratios and 90% confidence intervals (90% CI) were 1.29 (0.99 to 1.68), 1.43 (1.14 to 1.81), and 1.60 (1.35 to 1.90) for t_{max}, C_{max} and AUC, respectively. This represents 43% and 60% increase in Cmax and AUC, respectively. By contrast, sirolimus did not affect the C_{max} and $AUC_{0\text{-}24h}$ of diltiazem. The GLS mean ratios (90% CI) of C_{max} and AUC for diltiazem were 1.01 (0.90 to 1.13) and 1.05 (0.95 to 1.15), respectively. The t_{max} of diltiazem was slightly affected by sirolimus as shown by the GLS mean ratio (90% CI) of 0.87 (0.78 to 0.98). There were no effects of sirolimus on the t_{max}, C_{max}, and AUC_t of diltiazem metabolites, desacetyldiltiazem and desmethyldiltiazem. It is recommended that caution should be exercised if it is at all necessary to administer sirolimus with diltiazem.

Ketoconazole: Investigation of the potential pharmacokinetic interaction between sirolimus (single dose) and ketoconazole (multiple dose) was based on a non-randomized, 2-period, cross over (sirolimus) study in 24 healthy adults. In period I, study subjects received a single 5-mg oral dose of sirolimus. During period II, subjects received ketoconazole 200-mg daily on days 1 to 10, and a 5-mg dose of sirolimus was administered concomitantly with ketoconazole on day 5. Ketoconazole affected both the rate and extent of absorption of sirolimus. There was an increase in sirolimus exposure in blood as reflected by GLS mean ratios (and 90% CI) of 4.42 (3.77 to 5.17) for C_{max} and 10.9 (9.19 to 13.0) for AUC. This represented an increase of Cmax and AUC of 332% and 990%, respectively. The apparent oral clearance (CL/F) was decreased 91.5%. Sirolimus t_{max} was increased by 38% and $t_{1/2}$ was not significantly affected. The findings in this study suggest that the increase in sirolimus oral bioavailability during ketoconazole administration is most likely due to the inhibitory effect of ketoconazole on intestinal CYP3A4 and/or P-gp. Single dose of sirolimus did not affect the pharmacokinetics of ketoconazole.

Because of the magnitude of the interaction and the large variability observed, it is suggested that other azole antifungals with little or noinhibitory potential on cytochrome P450 3A4 isozyme be considered if an anti-fungal therapy is needed while patient is receiving sirolimus. It is recommended that sirolimus should not be coadministered with ketoconazole.

Rifampin: Investigation of the potential interaction between sirolimus (single dose) and rifampin (multiple dose) was based on non-randomized, two-period study in healthy volunteers. During period I, subjects received a single 20- mg oral dose of sirolimus. During period II, subjects received daily doses of rifampin 600-mg on days 1 to 14, and a concomitant 20-mg dose of sirolimus on day 9.

Co-administration of sirolimus with rifampin dramatically reduced sirolimus exposure in whole blood as reflected by GLS mean ratios (90% CI) of 0.29 (0.26 to 0.32) and 0.18 (0.16 to 0.21) for C_{max} and AUC, respectively. The GLS mean ratio (90% CI) for weight-normalized CL/F were 5.53 (4.74, 6.45). By contrast, sirolimus t_{max} and $t_{1/2}$ were not affected by rifampin oral administration. Whole blood sirolimus exposure was decreased by 82% without any concurrent changes in the terminal disposition $t_{1/2}$. These results are compatible with a reduction in sirolimus oral bioavailability during rifampin administration. Alternative therapy with a lesser or reduced induction potential than rifampin should be considered when necessary. Concentration-time data for rifampin were not determined. Hence, the effect of sirolimus on rifampin pharmacokinetics is not known.

Cyclosporine (Neoral): Investigation of the potential interaction between cyclosporine (Neoral®) and sirolimus was based on a randomized, four-period, crossover study in healthy volunteers. All subjects received a single 10-mg dose of sirolimus, a single 300-

mg dose of cyclosporine, simultaneous single-dose sirolimus (10 mg) and cyclosporine (300 mg), and staggered single-dose co-administration of the two drugs (sirolimus 4 hours after cyclosporine). The following table contains the ratios of the various treatments. The rate and extent of absorption of sirolimus were both significantly affected after both simultaneous and staggered administration with Neoral. Co-administration of cyclosporine and sirolimus did not affect the pharmacokinetics of cyclosporine after either simultaneous or staggered administration.

The GLS mean ratios and 90% CIs for the sirolimus pharmacokinetic parameters are given in the

Table 9: GLS MEAN RATIOS AND 90% CONFIDENCE INTERVALS FOR SIROLIMUS PHARMACOKINETIC PARAMETERS

	Simultaneous Sirolimus + CsA		Staggered Sirolimus + CsA	
Parameter	Ratio[a]	90% CI	Ratio[b]	90% CI
C_{max}	1.92	1.53, 2.31	1.58	1.18, 1.98
t_{max}	2.16	1.98, 2.37	1.37	1.25, 1.51
$t_{1/2}$	0.97	0.83, 1.15	1.10	0.94, 1.30
AUC	3.30	2.96, 3.68	1.80	1.61, 2.01
CL/F/WT	0.30	0.27, 0.34	0.56	0.50, 0.62

a: (Simultaneous sirolimus + CSA):(sirolimus alone)
b: (sirolimus 4-h After CsA):(sirolimus Alone)

There was no significant difference in the pharmacokinetic parameters of sirolimus except for Tmax, which increased after the simultaneous and staggered administration by 17% and 16%, respectively. It is recommended that if sirolimus is administered with Neoral, it should be given 4 hours after Neoral.

Table 10

MEAN ± SD WHOLE BLOOD CSA PHARMACOKINETIC PARAMETERS

Treatment	Statistic	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (ng·hr/mL)	CL/F/WT (mL/hr/kg)
CSA	Mean	1.50	1560	12.7	7640	558
Alone	SD	0.59	292	2.5	1470	102
CsA +Sirolimus	Mean	1.64	1640	12.8	7930	536
Simultaneous	SD	0.66	414	3.8	1600	112
CSA + Sirolimus	Mean	1.64	1450	12.5	7040	608
Staggered[a]	SD	0.66	329	1.8	1520	122

a: sirolimus 4 hours after CsA

Cycosporine liquid (Sandimmune®): Investigation of the potential effect of cyclosporine (Sandimmune®) on the pharmacokinetics of sirolimus was based on a comparison of the whole blood sirolimus average trough concentrations in 150 psoriasis patients receiving sirolimus alone or a combination of sirolimus and Sandimmune®. Patients were randomized to treatment groups for sirolimus alone were administered 0.5, 1.5, and 3.0 mg/m^2 oral doses of sirolimus. Patients randomized for combination therapy received in a randomized fashion the same sirolimus doses administered to those who

received sirolimus alone but each patient also received a concomitant 1.25 mg/kg oral dose of CsA. The increase in average sirolimus trough concentrations for the 0.5, 1.5, 3.0 mg/m^2 were 63%, 80% and 72%, respectively, when compared to when sirolimus was administered without cyclosporine. The intersubject variability (%CV) for sirolimus trough concentrations ranged from 39.7 to 68.7%.

There was no significant effect of single or multiple dose sirolimus on cyclosporine liquid (Sandimmune®) trough concentrations. However, the interpatient variability (%CV) was very large, ranging from 85.9% to 165%. The effect of liquid cyclosporine (Sandimmune®) on sirolimus is not conclusive from this study in psoriasis patients and additional study is needed to determine the magnitude of changes in sirolimus concentrations. In addition, it is recommended that the applicant study the interaction between sirolimus and other formulations of cyclosporine (e.g. SangCya) to determine the effect of these formulations on sirolimus and vice versa. It is recommended that sirolimus concentrations be monitored if it is to be administered with Sandimmune®. Cyclosporine oral solution, USP, (Sandimmune®) is not bioequivalent to cyclosporine soft gelatin capsules, USP (Modified) (Neoral®) and should not be used interchangeably.

The following table provides a summary of the potential effects of some concomitantly administered drugs on the pharmacokinetics of sirolims.

Table 11 GLS MEAN RATIOS OF SIROLIMUS PHARMACOKINETIC PARAMETERS AFTER CO-ADMINISTRATION WITH POTENTIALLY INTERACTING DRUGS

Subject Type	Interacting Drug	Ratio of Sirolimus Pharmacokinetic Parameter[a,b,c]				
		t_{max}	C_{max}	$t_{1/2}$	AUC	CL/F/WT
Healthy Volunteers	Diltiazem	1.29	1.43	0.85	1.60	0.38
	Ketoconazole	1.38	4.42	↔	10.9	0.085
	Acyclovir	0.95	↔	↔	↔	↔
	Glyburide	↔	↔	↔	↔	↔
	Nifedipine	↔	↔	↔	↔	↔
	Digoxin	1.03	↔	↔	↔	↔
	Lo/Ovral®	-	-	0.86	1.08	↔
	Rifampin	↔	0.29	↔	0.18	5.53
	Neoral® (simultaneous)	1.92	2.16	↔	3.30	0.30
	Neoral® (staggered)	1.58	1.37	1.10	1.80	0.56
Renal Post-Transplant	Bactrim®	↔	↔	-	↔	-
Psoriasis	Sandimmune® (simultaneous)	-	-	-	1.75[d]	-

a: 90% CI of the ratios do not lie within the 0.80 to 1.25 equivalence window
b: Ratio = (sirolimus + drug): (sirolimus alone)
c: ↔ = 90% CI of the ratios are within the range of 0.80 to 1.25
d: Ratio of average sirolimus trough concentrations

A summary of the potential effects of sirolimus on the pharmacokinetics of some concomitantly administered drugs is given in the following table

Figure 10

COMPARATIVE SIROLIMUS EXPOSURE AMONG PHASE I DRUG-INTERACTION STUDIES

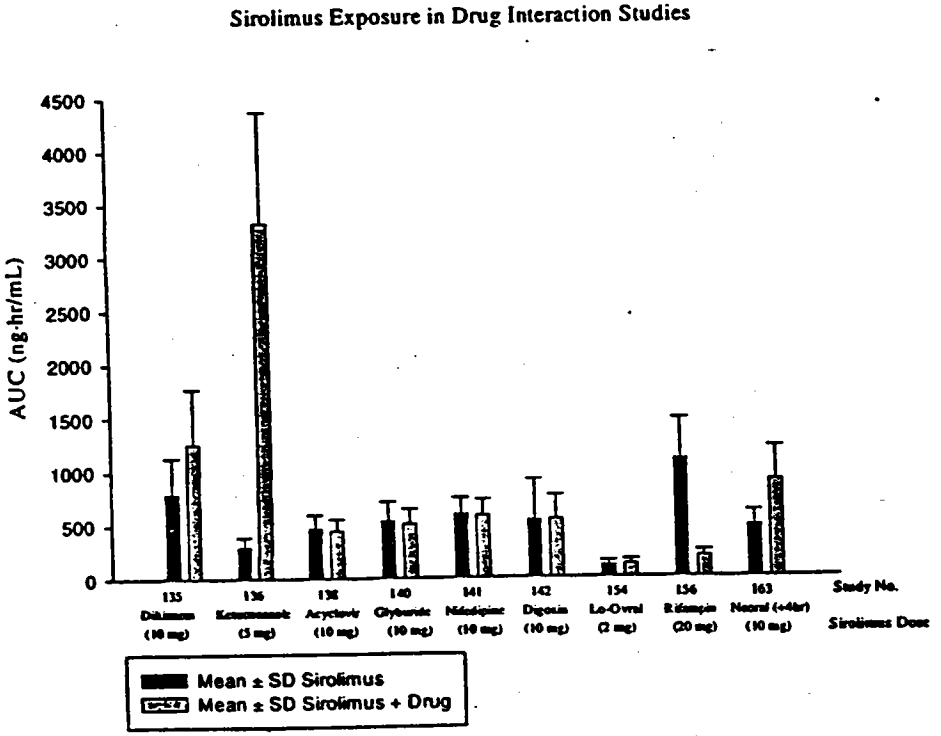


Table 12 LS MEAN RATIOS OF PHARMACOKINETIC PARAMETERS OF POTENTIALLY INTERACTING DRUGS AFTER CO-ADMINISTRATION WITH SIROLIMUS[a,b]

Subject Type	Interacting Drug	Dose Regimen	Ratio of Pharmacokinetic Parameter[c]				
			t_{max}	C_{max}	$t_{1/2}$	AUC	CL/F/WT
Healthy Volunteers	Diltiazem	SD	0.87	↔	-	↔[d]	-
	Desacetyldiltiazem		↔	↔	-	↔[d]	-
	Desmethyldilatiazem		0.90	↔	-	↔[d]	-
	Acyclovir	MD	1.05	↔	-	↔	↔
	Glyburide	SD	1.10	1.20	-	↔	-
	Nifedipine	SD	1.14	0.84	-	0.87[d]	-
	Digoxin	MD	1.24	↔	-	↔	-
	Lo/Ovral®	MD					
	Ethinyl Estradiol		1.41	0.88	-	↔	-
	Norgestrel		0.92	↔	-	↔	-
	Rifampin	MD	-	-	-	-	-
	Neoral® (simultaneous)	SD	1.17	↔	↔	↔	↔
	Neoral® (staggered)	SD	1.16	↔	↔	↔	↔
Renal Post-Transplant	Neoral® (staggered)	MD	↔[e]	↔[e]	-	1.15[e]	0.64[e]

a: 90% CI of ratios do not lie with in the 80 to 125% bioequivalence window
b: Ratio = (drug +sirolimus)/ (drug alone)
c: ↔ = 90% CI of the ratios are within the range 0.80-1.25
d: AUC over 0 to 48h
e: Ratio of mean values for (sirolimus treatment groups)/ (placebo group)

The applicant provided studies that evaluated the pharmacokinetic interaction of sirolimus with possible drugs that could be coadministered to patients. Other possible classes of compounds not evaluated were the macrolides (e.g. erythromycin, clarithromycin) and protease inhibitors (e.g. ritonavir, indinavir) which are known to be inhibitors and/or substrates for CYP3A4. Therefore, extreme caution should be exercised if these compounds are coadministered with sirolimus.

Label: Please refer to the final printed label; labeling comments are incorporated in the final negotiated label.

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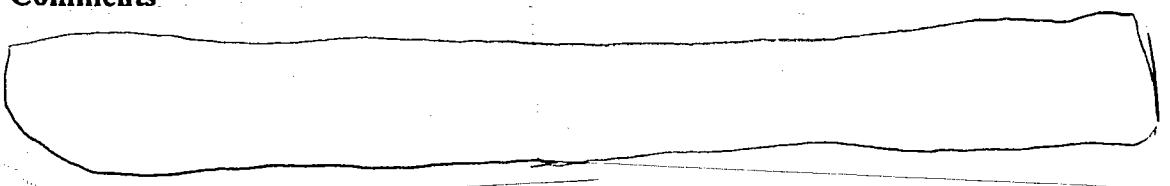
Comments



2) To better define an adequate time of dosing of sirolimus with respect to cyclosporine administration, it is recommended that the sponsor evaluate in a study various times when sirolimus and cyclosporine administration could be staggered. This study will provide a better understanding of the magnitude of sirolimus increase if patients do not comply with taking sirolimus 4-hour after the cycclosporine dose.

3) The sponsor should consider conducting additional drug-drug interaction study with drugs metabolized by CYP 3A4, especially macrolides and protease inhibitors

4) It is recommended that the sponsor conduct *in vitro* studies to better define the effect of the p-glycoprotein efflux system on sirolimus pharmacokinetics.

5) It is recommended that the applicant further evaluate, in future clinical studies, the effect of ethnicity on the pharmacokinetics of sirolimus. This will facilitate the determination of the optimum dosing regimen in patients from other ethnic origin.

6) It is recommended that the applicant validate the optimum therapeutic concentration range for sirolimus and further evaluate the value of reduced CsA concentrations in combination with sirolimus as suggested by the logistic regression modeling exercise. The evaluation could be done in a small clinical study or if feasible in planned future clinical studies employing therapeutic drug monitoring. This will facilitate the determination of the optimum dosing regimen for sirolimus in renal transplant patients.

Recommendation

The studies submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21,083 to fulfil sections 320 and 201.5 of 21 CFR are acceptable and support a recommendation for approval.

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/S/ 8/11/99

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