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APPLICATION NUMBER:

50-722/S-007

50-723/S-004

50-759/S-005

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

NDA: 50-722 (S-007)

50-723 (S-004)

50-759 (S-005)

Submission Date: 2/18/00, 4/20/00, 11/30/00, 12/12/00

Generic Name: Mycophenolate Mofetil

Brand Name: Cellcept®

Date Assigned: 3/1/00

Applicant: Roche

Final Review: 12/19/00

Submission Code: S

Reviewer: Kofi A. Kumi, Ph.D.

Executive Summary

The applicant submitted a supplemental New Drug Application (NDA) to extend the current use of Cellcept (mycophenolate mofetil, MMF) in the prophylaxis of acute rejection to pediatric patients receiving allogeneic renal transplants. The applicant's premise for development of Cellcept for pediatric renal transplant patients is that the course of acute rejection and the mechanism of action of Cellcept in the prevention of acute rejection are sufficiently similar in adults and pediatric populations to permit extrapolation from the adult efficacy data to the pediatric patients. Hence, the submission primary focused on the safety and pharmacokinetics after Cellcept administration in pediatric renal transplant patients.

The pivotal pediatric study was a 3-year study with a 12-month interim analysis performed when the last patient enrolled achieved 1 year post-transplant. This is a 12-month interim report. This was designed as an open-label, single-arm study, in which MMF was added to standard immunosuppressive therapy (cyclosporine and prednisone) for pediatric recipients of a first or second renal allograft. The MMF dose used in the pivotal pediatric study (MYCS2675) was selected based on previous pediatric renal transplant study (MYC2190) and a consideration of the safety, efficacy and pharmacokinetic data obtained from primary controlled adult renal transplant study. In the original NDA review, there was a suggestion that the pharmacokinetic parameter that best predicted allograft renal rejection is MPA AUC. Based on the controlled adult renal transplant patients data, the target mean MPA AUC during the early post-transplant period to prevent rejection was determined to be $27.2 \mu\text{g}\cdot\text{h}/\text{mL}$. A dose of $600 \text{ mg}/\text{m}^2$ (up to 1 g) bid was selected for the pivotal pediatric pharmacokinetic study. All clinical trials in the human pharmacokinetic section of the application were performed using the suspension or capsule dosage formulations of MMF. The suspension is bioequivalent to the capsule formulation.

The primary questions the reviewer focused on during the review were 1) What was the exposure AUC(0-12h) after administration of Cellcept $600 \text{ mg}/\text{m}^2$ and is this similar to the target AUC(0-12) of about $27.2 \mu\text{g}\cdot\text{hr}/\text{mL}$ during the early post transplant period? 2) Are there any age related differences in the pharmacokinetics of MPA? 3) How does the pharmacokinetics in pediatric renal transplant patient compare to adult renal transplant patients 4) Is AUC(0-12h) the best predictor of acute rejection in pediatric transplant patients 5) Are there gender or race differences in the pharmacokinetics of MPA in pediatric transplant patients?

What was the exposure (AUC(0-12h)) after administration of Cellcept 600 mg/m² and is this similar to the target AUC(0-12) of about 27.2 µg*hr/mL during the early post transplant period?

The day 7 MPA pharmacokinetic parameters are provided in the following table. Mean MPA AUC is presented graphically figures 1-3 (pages 6-8)

Table 1: Mean Computed Pharmacokinetic Parameters for MPA by Age and Time (Day 7)

Age-Group (n)	Tmax (h)	Cmax (µg/mL) ^a	AUC(0-12) (µg*h/mL) ^a
< 6 years (17)	1.63 ± 2.85	13.2 ± 7.16	27.4 ± 9.54
6 – 12 years (16)	0.940 ± 0.546	13.1 ± 6.30	33.2 ± 12.1
12- 18 years (21)	1.16 ± 0.830	11.7 ± 10.7	26.3 ± 9.14
< 2 year ^b (6)	3.03 ± 4.70	10.3 ± 5.80	22.5 ± 6.68

^aCmax and AUC were adjusted to a dose of 600 mg/m²

^bThe <2 years is a subset of the < 6 year

The mean MPA parameters observed in the pivotal study were similar across the age groups of < 6 years, 6 - <12 years and 12 – 18 years. The mean dose-adjusted MPA AUC(0-12) for all patients on day 7 for the three age groups were similar to the target mean MPA AUC(0-12) of 27.2 µg*hr/mL. In a subgroup analysis of the < 6 year old group, the exposures (AUC(0-12)) in 0-2 year olds appeared to be lower than those of the other age groups. The mean MPA AUC (0-12) was lower (22.7 µg*h/mL). Cmax was lower for the <2 year old patients on day 7. There was a wide degree of variability and the sample size was small (n=6).

Are there any age related differences in the pharmacokinetics of MPA?

The mean MPA parameters were similar across the age groups of < 6 years, 6 - <12 years and 12 – 18 years except for the month 9 mean dose-adjusted MPA Cmax which decreased by age group. The mean dose-adjusted MPA and MPAG PK parameters were similar across the age groups of < 6 years, 6 - <12 years and 12 – 18 years except for the month 9 mean dose-adjusted MPA Cmax which decreased by age group and the mean dose-adjusted MPAG which increased by age group. The mean dose adjusted MPA AUC(0-12) for the 6 - < 12 age group was about 22% greater than the target from adult data (Figures 1-3). In a subgroup analysis of the < 6 year old group in both the pivotal (n=6) and pilot (n = 1) study, the < 2year old (actually none of the patients were less than 1 year old) the exposures (AUC(0-12)) appeared to be lower than those of the other age groups; Cmax was lower for the <2 year old patients on day 7 but not on month 3 and 9. The mean dose adjusted MPA AUC(0-12) was numerically lower (20.7 µg*h/mL) with a wide degree of variability (95% CI: 14.9 – 26.5 µg*hr/mL); however, the sample size was small (n=7) (Tables 2 – 3; pages 8m- 9).

How does the pharmacokinetics in pediatric and adult allograft renal transplant patients compare?

The pharmacokinetic data from adult transplant patients and the pharmacokinetic data obtained from the pediatric studies in both the early and late post-transplant periods were compared. AUC (0-12) and Cmax appeared similar between the study populations of pediatric and adult renal transplant patients in both the early and late period when Cellcept is administered 600 mg/m² bid up to 1 gm bid in pediatric patients and 1 gm bid in adult patients. By examining the mean MPA AUC (0-12) and 95% confidence intervals (CI) for various subgroups of pediatric patients to the

target MPA AUC (0-12), the pediatric and adult MPA AUC (0-12) were similar. The following table contains the pharmacokinetic parameters during the early post-transplant period for the adult patients who received 1 gm BID that is currently in the approved label

Table 4: Pharmacokinetic Parameters of MPA in Renal Transplant Patients

Time after Transplantation	Dosing Regimen (oral)	Tmax (h)	Cmax (µg/mL)	Total AUC (µg*h/mL)
6 days	1 gm BID (n=31)	1.33 ± 1.05	10.7 ± 4.83	32.9 ± 15.0
Early (< 40 days)	1 gm BID (n=25)	1.31 ± 0.76	8.16 ± 4.50	27.3 ± 10.9

Is AUC(0-12h) the best predictor of acute rejection in pediatric transplant patients

An exploratory pharmacokinetic/pharmacodynamic (PK/PD) evaluation was undertaken. Biopsy proven rejection within the first 6 months post transplant occurred in 12 of the 55 patients. For MPA AUC (0-12), Cmax and Cmin day 7 values were plotted by rejection or no rejection (figure 4). The following table provides the day 7 PK parameters for patients with and without rejection. Pediatric patients who had a biopsy proven rejection within 6 months post-transplant had day 7 PK parameters that are within the same range as those patients not experiencing a rejection. None of the PK parameters (Cmax, AUC and Cmin) was a good predictor of rejection in the pediatric study. The applicant speculated that the reasons a PK/PD evaluation was not observed included the fact that the study was not designed to evaluate a PK/PD relationship, a single dose level resulting in an expected narrow range of MPA AUC(0-12) values which may not have allowed for adequate spread of MPA AUC(0-12) values to distinguish the presence or absence of rejection. Also the day 7 PK parameters available for evaluation may not represent the true exposure at the time of rejection and the number of episodes was relatively small. The applicant's rationale for the lack of exposure-response is reasonable. One gm Cellcept BID has been shown to be effective in adult renal transplant patients and the exposures obtained for the pediatric renal transplants are similar to that observed in adults.

Table 5: Summary of Day 7 Pharmacokinetic Parameters (mean ± SD) by Mouth 6 Rejection Status in Pediatric Patients

PK Parameter	Rejection (n=12)	No Rejection (n=42)
AUC(0-12) (µg*h/mL)	26.5 ± 6.68 ^a	28.0 ± 10.7
Cmax (µg/mL)	11.5 ± 6.71	12.3 ± 8.42
Cmin (µg/mL)	0.754 ± 0.414	0.845 ± 0.637

^a n=11

Are there any gender or race differences in the pharmacokinetics of MPA in pediatric transplant patients?

Gender: When Cellcept suspension was given as 600 mg/m² bid up to 1 gm bid to males and females, 1 – 18 years of age, the day 7 mean dose adjusted MPA AUC(0-12) in females was similar to the target mean MPA AUC(0-12) and in males was slightly greater than the target mean MPA AUC. There was no significant difference in MPA and MPAG pharmacokinetic parameters between males and females at any time point except MPAG Cmax at month 9 (Table 6-7; page 11).

Race: The number of blacks enrolled in the pediatric studies (10 out of 92 pediatric patients) were too small to allow statistical comparison. Mean dose adjusted MPA AUC(0-12) and Cmax tended

to be lower in blacks at all timepoints. Both blacks and non-blacks had a mean dose adjusted AUC (0-12) similar to the targeted mean AUC(0-12); however, there was large variability for blacks. Mean MPAG PK values in blacks were numerically greater than non-blacks except at month 3 (Tables 8-9; page 12).

General Comments

The pharmacokinetics of MPA and MPAG after administration of Cellcept to pediatric patients between the ages of 1 to 18 years old were similar. However, less than 2 year old patients had exposures that were numerically lower than the other pediatric age groups studied and adult populations. There was wide variability and the number of patients were relatively small (n=7), hence a definitive conclusion as to the pharmacokinetics of MPA in this age group cannot be made. Due to the small number of patients in this age group that receive renal transplantation, it may not be feasible to adequately evaluate the pharmacokinetics in this age group. It is recommended the patients be closely monitored.

There is about 1.7-fold increase in AUC when day 7 values is compared to month 3 values. This is consistent to what was observed in adult renal transplant patients

In order to determine the appropriate dosing regimen of intravenous Cellcept in pediatric population, it is recommended that the applicant evaluate the pharmacokinetics of MPA and the tolerability of mycophenolate mofetil after intravenous Cellcept administration.

Recommendation

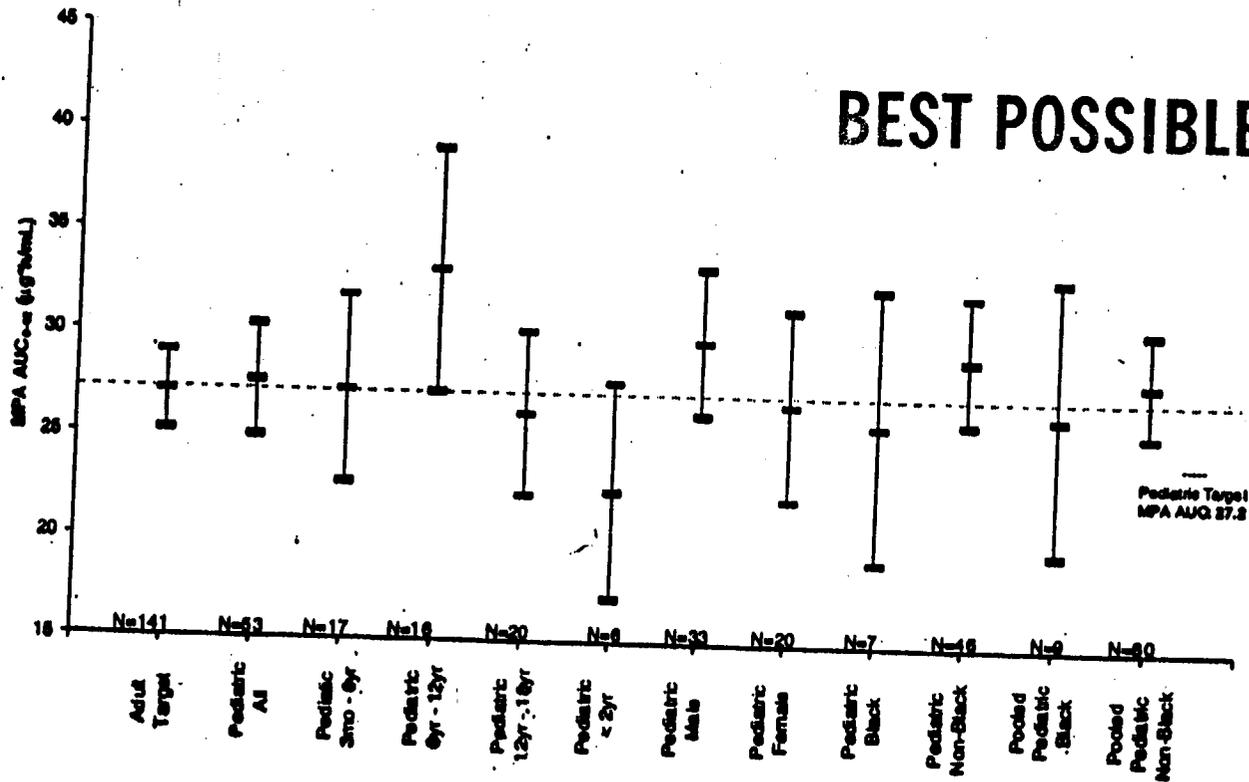
The pharmacokinetic information submitted to the Human Pharmacokinetics and Bioavailability section of NDA 50,722 (SE5-007) to fulfill sections 320 and 201.5 of CFR are acceptable and support a recommendation for approval.

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Figure 3

Mean and 95% Confidence Intervals for Day 7 Dose
 Pediatric Renal Transplant Patients and Adult Renal Transplant Patients in the
 Posttransplant Period



3

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Table 2

Mean \pm SD Computed MPA and MPAG PK Parameters By Age from Study MYCS2675 and Day 7
Data for all 7 Patients < 2 Years Old from Studies MYCS2675 and MYC2190

Age Group (n)	MPA			MPAG		
	T _{max} h	Adjusted ^a C _{max} µg/mL	Adjusted ^a AUC ₀₋₁₂ µg·h/mL (95% CI)	T _{max} h	Adjusted ^a C _{max} µg/mL	Adjusted ^a AUC ₀₋₁₂ µg·h/mL
Day 7						
3 mo -< 6yr (17)	1.63 \pm 2.85	13.2 \pm 7.16	27.4 \pm 9.54 (22.8 - 31.9)	2.41 \pm 2.70	60.8 \pm 30.5	378 \pm 205
6 - < 12 yr (16)	0.940 \pm 0.546	13.1 \pm 6.30	33.2 \pm 12.1 (27.3 - 39.2)	2.69 \pm 1.21	73.2 \pm 16.4	537 \pm 166
12 - 18 yr (21)	1.16 \pm 0.830	11.7 \pm 10.7	26.3 \pm 9.14 ^b (22.3 - 30.3)	2.61 \pm 1.32	76.6 \pm 37.9	685 \pm 417 ^c
All patients (54)	1.24 \pm 1.70	12.6 \pm 8.37	28.7 \pm 10.5 (25.9 - 31.6)	2.57 \pm 1.81	70.6 \pm 30.8	542 \pm 318
<2 yr (6)	3.03 \pm 4.70	10.3 \pm 5.80	22.5 \pm 6.66 (17.2 - 27.8)	3.60 \pm 4.41	46.8 \pm 19.8	260 \pm 85.9
<2 yr (7) ^d	2.67 \pm 4.39	9.54 \pm 5.71	20.7 \pm 7.80 (14.9 - 26.5)	3.37 \pm 4.07	43.1 \pm 20.5	237 \pm 98.3
Month 3						
3 mo -< 6yr (15)	0.989 \pm 0.511	22.7 \pm 10.1	49.7 \pm 18.2 (40.5 - 58.9)	2.96 \pm 1.76	65.2 \pm 21.5	475 \pm 178
6 - < 12 yr (14)	1.21 \pm 0.532	27.8 \pm 14.3	61.9 \pm 19.6 (51.6 - 72.1)	2.36 \pm 1.07	75.1 \pm 20.4	529 \pm 169
12 - 18 yr (17)	0.978 \pm 0.484	17.9 \pm 9.57	53.6 \pm 20.3 ^d (43.7 - 63.5)	2.93 \pm 1.68	86.5 \pm 36.9	790 \pm 402 ^d
All patients (46)	1.05 \pm 0.507	22.5 \pm 11.8	54.9 \pm 19.6 ^e (49.1 - 60.6)	2.75 \pm 1.53	76.1 \pm 28.6	602 \pm 304
<2 yr (4)	0.725 \pm 0.276	23.8 \pm 13.4	47.4 \pm 14.7 (33.0 - 61.8)	3.48 \pm 3.04	55.0 \pm 24.3	412 \pm 151
Month 9						
3 mo -< 6yr (12)	0.869 \pm 0.479	30.4 \pm 9.16	61.0 \pm 10.7 (54.9 - 67.0)	2.75 \pm 1.85	64.8 \pm 17.6	453 \pm 132
6 - < 12 yr (11)	1.12 \pm 0.462	29.2 \pm 12.6	66.8 \pm 21.2 (54.3 - 79.3)	2.20 \pm 0.918	76.2 \pm 22.4	546 \pm 181
12 - 18 yr (14)	1.09 \pm 0.518	18.1 \pm 7.29	56.7 \pm 14.0 (49.4 - 64.0)	2.85 \pm 1.12	84.2 \pm 24.2	680 \pm 212
All patients (37)	1.03 \pm 0.488	25.4 \pm 11.1	61.1 \pm 15.7 (56.0 - 66.2)	2.62 \pm 1.35	75.6 \pm 22.6	567 \pm 200
<2 yr (4)	0.604 \pm 0.208	25.6 \pm 4.25	55.8 \pm 11.6 (44.4 - 67.2)	3.48 \pm 3.00	61.1 \pm 23.8	445 \pm 94.5

^a adjusted to a dose of 600 mg/m²

^b data from study MYCS2675 day 7 (n=6) and study MYC2190 day 14 (n=1); patient in MYC2190 vomited on PK day

^c n=20

^d n=16

^e n=45

Table 3

[PK_sum_organ.pdf] Summary of MPA AUC and Cmax of Pediatric Renal, Adult Renal,

			AUC ₀₋₁₂ (µg·h/mL)	Cmax (µg/mL)
Pediatric Renal NYCS2190Y1 - 23mg/kg bid	Day 14	Mean	28.1	8.57
		Std.Dev	11.9	4.62
		%CV	42.2	54.0
		Min	3.77	2.59
		Max	45.7	20.9
		N	11	12
Pediatric Renal NYCS2675 - 600 mg/m2 bid	Day 21	Mean	32.9	12.8
		Std.Dev	14.8	13.9
		%CV	44.9	108.
		Min	12.0	3.27
		Max	68.9	52.6
		N	13	13
Pediatric Renal NYCS2675 - 600 mg/m2 bid	Day 7	Mean	27.7	12.1
		Std.Dev	9.98	8.02
		%CV	36.0	66.3
		Min	14.4	1.74
		Max	53.1	47.8
		N	53	54
	Month 3	Mean	49.9	20.1
		Std.Dev	19.3	10.2
		%CV	38.7	50.6
		Min	16.0	4.50
		Max	100.	45.2
		N	45	46
Month 9	Mean	54.5	22.4	
	Std.Dev	16.8	10.0	
	%CV	30.8	44.7	
	Min	18.2	6.43	
	Max	95.4	49.3	
	N	37	37	
Adult Renal 173,1866,2176,061,016,SSPK - 1.0 g bid	< Day 40	Mean	23.9	8.32
		Std.Dev	10.2	6.13
		%CV	42.7	73.7
		Min	7.49	1.44
		Max	59.8	49.2
		N	89	89
	> Month 3	Mean	43.6	16.1
		Std.Dev	23.6	8.06
		%CV	54.2	50.1
		Min	11.5	3.54
	Max	94.0	31.6	
	N	23.0	23.0	

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Table 6

MYCS2675: Summary of Mean MPA PK By Gender Over Time

Groups (n)	t_{max} (h)	Adjusted ^a C_{max} ($\mu\text{g/mL}$)	Adjusted ^a AUC_{0-12} ($\mu\text{g}\cdot\text{h/mL}$) and (95% Confidence Interval)
Day 7			
Female (20)	1.51 \pm 2.64	11.1 \pm 7.36	26.9 \pm 10.6 (22.2-31.5)
Male (34)	1.08 \pm 0.736	13.4 \pm 8.91	29.9 \pm 10.4 ^b (26.3-33.4)
p-value	-	-	-
Month 3			
Female (16)	0.882 \pm 0.470	22.6 \pm 13.2	53.1 \pm 18.2 (44.2-62.1)
Male (30)	1.14 \pm 0.510	22.4 \pm 11.3	55.8 \pm 20.5 ^c (48.3-63.3)
p-value	-	-	-
Month 9			
Female (12)	0.994 \pm 0.453	25.2 \pm 12.2	59.5 \pm 15.5 (50.7 - 68.3)
Male (25)	1.07 \pm 0.508	25.4 \pm 10.7	61.8 \pm 16.1 (55.5 - 68.1)
p-value	-	-	-

Mean \pm SD

p-value is not significant ($p < 0.05$) unless noted

^a adjusted to a dose of 600 mg/m²

^b n=33

^c n=29

Table 7

MYCS2675: Summary of Mean MPAG PK By Gender Over Time

Groups (n)	t_{max} (h)	Adjusted ^a C_{max} ($\mu\text{g/mL}$)	Adjusted ^a AUC_{0-12} ($\mu\text{g}\cdot\text{h/mL}$)
Day 7			
Female (20)	2.64 \pm 2.58	68.1 \pm 39.5	547 \pm 450
Male (34)	2.54 \pm 1.20	72.1 \pm 24.9	538 \pm 209 ^b
p-value	-	-	-
Month 3			
Female (16)	3.02 \pm 2.19	67.6 \pm 29.2	536 \pm 356
Male (31)	2.61 \pm 1.07	80.4 \pm 27.8	638 \pm 272 ^c
p-value	-	-	-
Month 9			
Female (12)	2.92 \pm 1.88	64.8 \pm 24.7	507 \pm 208
Male (25)	2.48 \pm 1.01	80.7 \pm 20.1	595 \pm 194
p-value	-	0.043	-

Mean \pm SD

p-value is not significant ($p < 0.05$) unless noted

^a adjusted to a dose of 600 mg/m²

^b n=33

^c n=30

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Summary MPA PK By Racial Subgroup in MYCS 2675

Racial Subgroup (n)	$t_{1/2}$ (h)	Adjusted ^a C_{max} ($\mu\text{g/mL}$)	Adjusted ^a AUC_{0-12} ($\mu\text{g}\cdot\text{h/mL}$) (range)		95% CI
			Mean \pm SD	Range	
Day 7					
black (7)	1.07 ± 0.447	9.05 ± 4.81	25.9 ± 9.01		19.2-32.6
nonblack (47)	1.27 ± 1.81	13.1 ± 8.69	29.2 ± 10.7^b		26.1-32.3
Month 3					
black (6)	1.10 ± 0.583	15.5 ± 9.97	40.3 ± 9.26		32.9-47.7
nonblack (40)	1.04 ± 0.503	23.5 ± 11.8	57.1 ± 19.8^c		50.9-63.3
Month 9					
black (5)	1.20 ± 0.754	18.7 ± 7.37	54.3 ± 8.05		47.2-61.4
nonblack (32)	1.00 ± 0.445	26.4 ± 11.3	62.1 ± 16.4		56.5-67.8

Mean \pm SD

^a adjusted to a dose of 600 mg/m²

^b n=46

^c n=39

Table 9

Summary MPAG PK By Racial Subgroup in MYCS2675

Racial Subgroup (n)	$t_{1/2}$ (h)	Adjusted ^a C_{max} ($\mu\text{g/mL}$)	Adjusted ^a AUC_{0-12} ($\mu\text{g}\cdot\text{h/mL}$)
Day 7			
black (7)	2.63 ± 1.31	77.7 ± 26.1	627 ± 260
nonblack (47)	2.56 ± 1.89	69.5 ± 31.5	528 ± 326^b
Month 3			
black (7)	2.66 ± 1.27	58.9 ± 16.9	462 ± 142
nonblack (40)	2.77 ± 1.59	79.1 ± 29.3	627 ± 319^c
Month 9			
black (5)	3.10 ± 1.24	82.4 ± 22.2	627 ± 227
nonblack (32)	2.55 ± 1.37	74.5 ± 22.9	557 ± 198

Mean \pm SD

^a adjusted to a dose of 600 mg/m²

^b n=46

^c n=39

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12/19/00

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NDA 50,722 SE5-007 (Original)

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REVIEW

Background

Cellcept (Mycophenolate mofetil, MMF) was originally approved in 1995 for prophylaxis of acute rejection in adult renal transplant patients under NDA 50,722. The current recommended dose is 1 gm bid. A dosing regimen 1.5 gm bid is reported to be effective but it has higher adverse effects compared to 1 gm bid with no clear advantage in terms of efficacy over the 1 gm bid dosing regimen. MMF is completely absorbed and rapidly converted to MPA, the active moiety of MMF. Mean Cmax and AUC(0-12) values increase 1.7 and 1.8-fold, respectively between the early post-transplant period to 3 months post-transplant. The adult data used in the safety and efficacy comparisons with pediatric data are derived from patients who received MMF 1gm bid.

The age stratification of infants and young children in the pediatric studies differs from the age stratification of infants and young children adopted from the agencies' guidelines. Patients exceeding the upper age limit of these guidelines (> 16 years of age) were included in the MMF pediatric age. A subgroup analysis for under 2 years was requested by the agency and conducted by the applicant.

The pivotal pediatric study was a 3-year study with a 12-month interim analysis performed when the last patient enrolled achieved 1 year post-transplant. This is a 12-month interim report. This was designed as an open-label, single-arm study, in which MMF was added to standard immunosuppressive therapy (cyclosporine and prednisone) for pediatric recipients of a first or second renal allograft. The MMF dose used in the pivotal pediatric study (MYCS2675) was selected based on previous pediatric renal transplant study (MYC2190) and a consideration of the safety, efficacy and pharmacokinetic data obtained from primary controlled adult renal transplant study. In the original NDA review, there was a suggestion that the pharmacokinetic parameter that best predicted allograft renal rejection is MPA AUC. Based on the controlled adult renal transplant patients data, the target mean MPA AUC during the early post-transplant period to prevent rejection was determined to be 27.2 $\mu\text{g}\cdot\text{h}/\text{mL}$. A dose of 600 mg/m^2 (up to 1 g) bid was selected for the pivotal pediatric pharmacokinetic study. All clinical trials in the human pharmacokinetic section of the application were performed using the suspension and capsule dosage forms of MMF suspension and capsules. The suspension is bioequivalent to the capsule formulation.

Overview of Pharmacokinetic Studies

Pivotal Study

Study Title (MYCS 2675): An Open-Label, safety, tolerance and pharmacokinetic study of oral mycophenolate mofetil (MMF) suspension in the prophylaxis of rejection in pediatric renal allograft recipients.

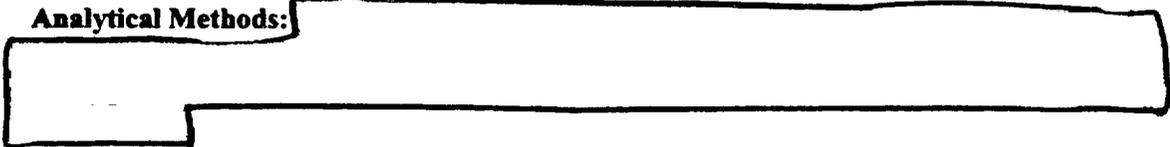
Objective: To evaluate the safety, tolerability and pharmacokinetics of mycophenolate mofetil oral suspension in combination with cyclosporine and corticosteroids in the prophylaxis of acute rejection in pediatric renal allograft recipients.

Study Design: This was a multi-center, open-label, single arm study. Patients were categorized to one of three defined age groups for observation over a three year period post-transplant, including follow-up after premature withdrawal from the study. Enrollment of 100 patients was planned, to obtain at least 75 patients completing 6 months on study drug. Fifty-five patients participated in

the PK portion of the study. The age groups studied were less than 6 years, 6 to less than 12 years and 12 to 18 years. The dose of MMF used in the study was 600 mg/m² bid, up to a maximum of 1 g bid. MMF was used concomitantly with cyclosporine and corticosteroids. At least 12 patients per age group underwent PK evaluation through 9 months post-transplant. MMF suspension was administered orally or enterally. Blood samples for pharmacokinetic analysis was collected on days 7, end of month 3, 9, 24 and 36. Pharmacokinetic sampling were taken at 0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 4.0, 8.0 and 12.0 hours post dosing on each scheduling sampling. The dose was administered after an overnight fast of at least 10 hours. Patients were not permitted to take antacids on PK sampling days. Blood samples were requested for PK analysis during a serious adverse event or acute rejection episode (PKAE)

Three formulations of MMF were used, two for oral suspension and one for 250 mg capsules. The only difference between the two oral suspension formulations was the presence of a colorant in one of them.

Analytical Methods:



Data Analysis: Pharmacokinetic parameters were obtained from plasma concentrations of MPA and MPAG collected over 12 hours on day 7, month 3 and month 9 using non-compartmental methods. Tmax, dose adjusted AUC(0-12) and dose adjusted Cmax on day 7, month 3 and month 9 were considered the primary PK parameters. Pharmacokinetic parameters, actual sampling times, and plasma concentrations were summarized by age group, gender and race for the three time periods. Data were compared for age group, racial subgroup (black and nonblack), and gender.

Results: The mean (range) MMF dose for all patients at day 7, month 3 and month 9 were 581 [redacted] mg/m² bid, 544 [redacted] mg/m² and 533 [redacted] bid, respectively. Eighty-one of 100 patients received study drug for at least six months, and 71 patients were on study drug for a minimum of 1 year. Fifty-five patients participated in the pharmacokinetic study

The pharmacokinetic parameters for MPA by age groups and time are provided in the following tables and figures on pages 23 – 30.

Mean Computed Pharmacokinetic Parameters for MPA by Age and Time (Day 7)

Age Group (n)	Tmax (h)	Cmax (µg/mL) ^a	AUC(0-12) (µg*h/mL) ^a
< 6 years (17)	1.63 ± 2.85	13.2 ± 7.16	27.4 ± 9.54
6 – 12 years (16)	0.940 ± 0.546	13.1 ± 6.30	33.2 ± 12.1
12- 18 years (21)	1.16 ± 0.830	11.7 ± 10.7	26.3 ± 9.14
< 2 year ^b (6)	3.03 ± 4.70	10.3 ± 5.80	22.5 ± 6.68

^aCmax and AUC were adjusted to a dose of 600 mg/m²

The <2 years is a subset of the < 6 year

Mean Computed Pharmacokinetic Parameters for MPA by Age and Time (Month 3)

Age Group	Tmax (h)	Cmax ($\mu\text{g/mL}$) ^a	AUC(0-12) ($\mu\text{g}\cdot\text{h/mL}$) ^a
< 6 years (15)	0.989 \pm 0.511	22.7 \pm 10.1	49.7 \pm 18.2
6 – 12 years (14)	1.21 \pm 0.532	27.8 \pm 14.3	61.9 \pm 19.6
12- 18 years (17)	0.978 \pm 0.484	17.9 \pm 9.57	53.6 \pm 20.2
< 2 year ^b (4)	0.725 \pm 0.484	23.8 \pm 13.4	47.4 \pm 14.7

^aCmax and AUC were adjusted to a dose of 600 mg/m²

The <2 years is a subset of the < 6 year

Mean Computed Pharmacokinetic Parameters for MPA by Age and Time (Month 9)

Age Group	Tmax (h)	Cmax ($\mu\text{g/mL}$) ^a	AUC(0-12) ($\mu\text{g}\cdot\text{h/mL}$) ^a
< 6 years (12)	0.869 \pm 0.479	30.4 \pm 9.16	60.9 \pm 10.7
6 – 12 years (11)	1.12 \pm 0.462	29.2 \pm 12.6	66.8 \pm 21.2
12- 18 years (14)	1.069 \pm 0.518	18.1 \pm 7.29	56.7 \pm 14.0
< 2 year ^b (4)	0.604 \pm 0.208	25.6 \pm 4.25	55.8 \pm 11.6

^aCmax and AUC were adjusted to a dose of 600 mg/m²

The <2 years is a subset of the < 6 year

MMF suspension given to patients 1 to 18 years of age produced no statistically significant differences ($p < 0.05$) in mean MPA plasma concentrations or in mean computed parameters between the three age groups, with the exception of dose adjusted Cmax at month 9 in the oldest group. The mean dose-adjusted MPA AUC(0-12) for the <6 and 12 – 18 year groups was similar to the targeted MPA AUC(0-12); however, the mean dose adjusted MPA AUC(0-12) for the 6 < 12 year group was about 22% greater than the target concentration. The values for mean calculated MPA PK parameters in the < 2 year age were similar to those of the other age groups. The mean MPA AUC (0-12) was numerically lower (22.5 $\mu\text{g}\cdot\text{h/mL}$) than the target mean MPA AUC (0-12) with a wide degree of variability. Mean dose adjusted MPA AUC (0-12) increased over time for all age groups; between day 7 and month 3 mean dose-adjusted MPA AUC (0-12) was 1.9-fold higher; the increase was 1.11-fold between months 3 and 9. The increases are similar to those observed in adult renal transplant patients.

The pharmacokinetic parameters for MPAG for the different age groups and time are provided in the following tables.

Mean Computed Pharmacokinetic Parameters for MPAG by Age and Time (Day 7)

Age Group (n)	Tmax (h)	Cmax ($\mu\text{g/mL}$) ^a	AUC(0-12) ($\mu\text{g}\cdot\text{h/mL}$) ^a
< 6 years (17)	2.41 \pm 2.70	60.8 \pm 30.5	378 \pm 205
6 – 12 years (16)	2.69 \pm 1.21	73.2 \pm 16.4	537 \pm 166
12- 18 years (21)	2.61 \pm 1.32	76.6 \pm 37.9	685 \pm 417
< 2 year ^b (6)	3.60 \pm 1.68	46.8 \pm 19.8	260 \pm 85.9

^aCmax and AUC were adjusted to a dose of 600 mg/m²

The <2 years is a subset of the < 6 year

Mean Computed Pharmacokinetic Parameters for MPAG by Age and Time (Month 3)

Age Group	Tmax (h)	Cmax ($\mu\text{g}/\text{mL}$) ^a	AUC(0-12) ($\mu\text{g}\cdot\text{h}/\text{mL}$) ^a
< 6 years (15)	2.96 \pm 1.76	65.2 \pm 21.5	475 \pm 178
6 – 12 years (14)	2.36 \pm 1.07	75.1 \pm 20.4	529 \pm 169
12- 18 years (17)	2.93 \pm 1.68	86.5 \pm 36.9	790 \pm 402
< 2 year ^b (4)	3.48 \pm 3.04	55.0 \pm 24.3	412 \pm 151

^aCmax and AUC were adjusted to a dose of 600 mg/m²

The <2 years is a subset of the < 6 year

Mean Computed Pharmacokinetic Parameters for MPAG by Age and Time (Month 9)

Age Group	Tmax (h)	Cmax ($\mu\text{g}/\text{mL}$) ^a	AUC(0-12) ($\mu\text{g}\cdot\text{h}/\text{mL}$) ^a
< 6 years (12)	2.75 \pm 1.85	64.8 \pm 17.6	453 \pm 132
6 – 12 years (11)	2.20 \pm 0.918	76.2 \pm 22.4	546 \pm 181
12- 18 years (14)	2.85 \pm 1.12	84.2 \pm 24.2	680 \pm 212
< 2 year ^b (4)	3.48 \pm 3.00	61.1 \pm 23.8	445 \pm 94.5

^aCmax and AUC were adjusted to a dose of 600 mg/m²

The <2 years is a subset of the < 6 year

There was a statistically significant difference in mean dose adjusted MPAG AUC (0-12) across the age groups at all time points, with values increasing from youngest to the oldest groups. However, there was an overlap of the data due to the large standard deviations in three age groups. Patients in the < 2 year had numerically lower mean dose-adjusted MPAG AUC (0-12).

Effect of Gender: The pharmacokinetic parameters for females and males are provided in the following tables

Mean Computed Pharmacokinetic Parameters for MPA by Gender and Time (Day 7)

Age Group	Tmax (h)	Cmax ($\mu\text{g}/\text{mL}$) ^a	AUC(0-12) ($\mu\text{g}\cdot\text{h}/\text{mL}$) ^a
Male (n = 34)	1.08 \pm 0.736	13.4 \pm 8.91	29.9 \pm 10.4
Female (n=20)	1.51 \pm 2.64	11.1 \pm 7.36	26.9 \pm 10.6

^aCmax and AUC were adjusted to a dose of 600 mg/m²

Mean Computed Pharmacokinetic Parameters for MPA by Gender and Time (month 3)

Age Group	Tmax (h)	Cmax ($\mu\text{g}/\text{mL}$) ^a	AUC(0-12) ($\mu\text{g}\cdot\text{h}/\text{mL}$) ^a
Male (n = 29)	1.14 \pm 0.510	22.4 \pm 11.3	55.8 \pm 20.5
Female (n=16)	0.882 \pm 0.470	22.6 \pm 13.2	53.1 \pm 18.2

^aCmax and AUC were adjusted to a dose of 600 mg/m²

Mean Computed Pharmacokinetic Parameters for MPA by Gender and Time (month 9)

Age Group	Tmax (h)	Cmax (µg/mL) ^a	AUC(0-12) (µg*h/mL) ^a
Male (n = 25)	1.07 ± 0.508	25.4 ± 10.7	61.8 ± 16.1
Female (n=12)	0.944 ± 0.453	25.2 ± 12.2	59.5 ± 15.5

^aCmax and AUC were adjusted to a dose of 600 mg/m²

In female and males, MPA mean plasma concentration and mean PK parameters did not differ significantly at any time point. The day 7 mean MPA AUC(0-12) in females and males were similar to the target mean MPA AUC(0-12).

Effect of Race on MPA and MPAG PK: The pharmacokinetic parameters of MPA for blacks and non-blacks are provided in the following tables

Mean Computed Pharmacokinetic Parameters for MPA by Race and Time (Day 7)

Age Group	Tmax (h)	Cmax (µg/mL) ^a	AUC(0-12) (µg*h/mL) ^a
Black (n = 7)	1.07 ± 0.447	9.05 ± 4.81	25.9 ± 9.01
Non-Black (n= 46)	1.27 ± 1.81	13.1 ± 8.69	29.2 ± 10.7

^aCmax and AUC were adjusted to a dose of 600 mg/m²

Mean Computed Pharmacokinetic Parameters for MPA by Gender and Time (month 3)

Age Group	Tmax (h)	Cmax (µg/mL) ^a	AUC(0-12) (µg*h/mL) ^a
Black (n = 6)	1.10 ± 0.583	15.5 ± 9.26	40.3 ± 9.26 (n= 39)
Non-Black (n=40)	1.04 ± 0.503	23.5 ± 11.8	57.1 ± 19.8 (n = 39)

^aCmax and AUC were adjusted to a dose of 600 mg/m²

Mean Computed Pharmacokinetic Parameters for MPA by Gender and Time (month 9)

Age Group	Tmax (h)	Cmax (µg/mL) ^a	AUC(0-12) (µg*h/mL) ^a
Black (n = 5)	1.20 ± 0.754	18.7 ± 7.37	54.3 ± 8.05
Non-Black (n= 32)	1.00 ± 0.445	26.4 ± 11.3	62.1 ± 16.4

^aCmax and AUC were adjusted to a dose of 600 mg/m²

Blacks had numerically lower values for mean dose-adjusted MPA Cmax and AUC (0-12) than non-blacks. Both blacks and non-blacks had day 7 mean dose adjusted MPA AUC (0-12) similar to the target mean MPA AUC(0-12); however blacks had a wider 95% CI. The mean (95% CI) MPA AUC for blacks and non-blacks were 25.9 (19.2 – 32.6) and 29.2 (26.1 – 32.3), respectively of day 7. For month 3, the mean (95% CI) MPA AUC for blacks and non-blacks were 40.3 (32.9 – 47.7) and 57.1 (50.9 – 63.3), respectively. For month 9, the mean (95% CI) MPA AUC for blacks and non-blacks were 54.3 (47.2 – 61.4) and 62.1 (56.5 – 67.8), respectively.

Maintenance Immunosuppression: The great majority of patients received both cyclosporine and corticosteroids for the first six months of the study. The mean cyclosporine doses was highest at each visit for the youngest group at each visit and decreased with increasing age. Over time mean cyclosporine dose levels decreased for all age groups.

For the three age groups, the mean corticosteroid dose was highest in the < 6 year group, lowest of all for the < 2 year subset. The mean dose decreased with age and over time decreased for each age group, stabilizing at month 4.

Pharmacokinetic- Adverse Events: Pre-dose and post dose concentrations were collected for selected serious adverse events and for acute rejection episodes. The number of patients experiencing biopsy proven rejection (BPR) or presumptive rejection was reported by the sponsor to be similar across the age groups.

No association was observed between low concentrations of MPA and rejection, nor between elevated plasma concentrations of MPA and serious adverse events (SAEs).

The adverse events reported was evenly distributed among all age groups. GI disturbance was evenly distributed among age groups. Sepsis due to bacteremia was more prominent in the youngest group. The overall incidence of opportunistic infections were similar across age groups. The most frequent adverse events that were reported in the younger age group was diarrhea, leukopenia, sepsis and anemia.

Summary: The pharmacokinetic evaluation indicated that a dose of 600 mg/m² bid achieved the targeted early post transplant MPA AUC (0-12) of 27.2 µg*h/mL. There was approximately 1.9-fold increase in dose-adjusted MPA AUC (0-12) between day 7 and month 3, which is consistent with the increase observed in MPA AUC for adult patients receiving 1 gm BID. Between months 3 and 9, there was a 1.11-fold increase in AUC (0-12) and C_{max}. Gender and race exploratory evaluation did not reveal any significant differences between male and females and blacks and non-blacks. However, blacks tended to have lower exposures, especially in the early transplant period. There was a statistically significant difference in mean dose-adjusted MPAG AUC(0-12) by age group at all time points. The mean dose-adjusted MPAG AUC(0-12) for all pediatric age groups was lower than the mean observed in adults receiving 1 g bid.

The rate of biopsy proven rejection was similar across the age groups, with slightly lower rejection rates for the youngest patients. Nineteen percent of patients experienced rejection episodes; this is reported by the sponsor to be consistent with those observed in adult renal transplant patients receiving Cellcept 1g bid.

Reviewer's comments: The pharmacokinetic evaluation indicated that a dose of 600 mg/m² bid to pediatric patients provided exposures that were comparable to that observed in adult renal transplant patients receiving 1 gm BID. However, in the younger patients (<2 years), it appears AUC during the early transplant period was lower than other age groups. There was a larger variability observed in the lower aged patients than in older group. Consistent with observation with adult transplant patients, black patients during the early transplant period had numerically lower AUC than non-blacks. However, the number of black patients were relatively smaller compared to non-black. The dosing regimen selected is appropriate for pediatric patients. The lower AUC value observed for the <2 year old has been brought to the attention of the reviewing medical officer.

Study Title (Study IID/MYCC2190/USA): An Open-Label, Dose-Ranging Pharmacokinetic, Safety and Tolerance Study of Oral Mycophenolate Mofetil in the Prevention of Rejection in Pediatric Renal and Hepatic Allograft Recipients.

Background: This was a pilot study to determine the dose that will achieve the exposures observed in adult population. The study was originally submitted to NDA 50,722 and reviewed during the evaluation of that NDA. This is a brief summary of the study and conclusions from the study.

Objective: The primary objective was to assess in pediatric renal and hepatic allograft recipients the pharmacokinetics of oral mycophenolate mofetil during the first year of treatment and the safety throughout treatment for up to 3 years for each of three dose levels in each of three age groups

Study Design: Cellcept oral capsules and single intravenous infusion were to be administered in three dose levels (15, 23, and 30 mg/kg bid up to 1.5 gm bid) to each of three age groups (< 6 years, 6- 12 years and 12 - 18 years). Cellcept dosing was to begin within 24 hours of completion of transplant but no later than 120 hours post-transplant. Patients could also receive concomitant cyclosporine and steroids, but not azathioprine. On days 14 and 21, blood samples were obtained at 0 (predose), 0.5, 2, 4, 6, 8 and 12 hours for determination of MPA and MPAG concentrations. The IV portion of the study was removed from the trial after only 2 patients received IV on day 1.

Fourteen renal allograft recipients (8 male, 6 female; aged 2 - 18 years) with a cumulative time on treatment ranging from 6 to 166 days and no hepatic allograft recipients had enrolled by cutoff date. MMF for oral dosing was provided in 250 mg capsules.

Results: The following table provides MPA pharmacokinetic parameters for each dose and age group.

Mean Computed MPA PK Parameters By Age After Oral MMF Capsule Dosing at Three Dose Levels

Sampling Time (h)	Dose (mg/kg bid)	Tmax (h)	Cmax (µg/mL)	AUC(0-12) (µg*h/mL)
Day 14 (n)	15			
3 mo -< 6yr (7)		0.738 ± 0.590	5.69 ± 3.22	13.5 ± 8.76
6 - 12 yr (4)		1.27 ± 0.892	8.63 ± 5.56	19.9 ± 11.4
12 - 18 yr (7)		3.22 ± 4.56	13.4 ± 12.9	27.2 ± 11.3
3 mo < 6 yr (1)	23	2.62	8.18	28.1
6 -< 12 yr (4)		1.70 ± 0.800	8.70 ± 2.99	28.9 ± 12.3
12 - 18 yr (3)		0.833 ± 0.652	9.06 ± 6.28	28.2 ± 15.3
3 mo -< 6 yr (0)	30	-	-	-
6 - < 12 yr (5)		1.79 ± 1.68	13.3 ± 9.92	29.3 ± 7.17
12 - 18 yr (3)		2.56 ± 3.56	11.8 ± 4.29	38.4 ± 15.6

Mean Computed MPA PK Parameters by Age after Oral MMF Capsule Dosing at Three Dose Levels

Sampling Time (h)	Dose (mg/kg bid)	Tmax (h)	Cmax ($\mu\text{g/mL}$)	AUC(0-12) ($\mu\text{g}\cdot\text{h/mL}$)
Day 21 (n)	15			
3 mo -< 6yr (6)		0.850 \pm 0.849	5.73 \pm 3.61	13.6 \pm 6.85
6 - 12 yr (5)		1.18 \pm 1.48	11.2 \pm 6.45	20.6 \pm 6.86
12 - 18 yr (7)		0.738 \pm 0.560	10.8 \pm 6.93	26.3 \pm 9.79
3 mo < 6 yr (1)	23	2.00	7.34	29.2
6 -< 12 yr (5)		1.46 \pm 0.785	17.0 \pm 20.0	40.1 \pm 17.6
12 - 18 yr (6)		1.32 \pm 0.758	11.5 \pm 10.2m	31.1 \pm 11.4
3 mo -< 6 yr (0)	30	-	-	-
6 - < 12 yr (5)		1.37 \pm 1.27	7.06 \pm 3.24	29.7 \pm 13.9
12 - 18 yr (3)		1.31 \pm 0.756	9.51 \pm 4.94	42.4 \pm 23.4

There was large variability in the data and the small sample size, it was concluded that definite conclusions could not be drawn. However, it was suggested that 23 mg/kg provided the exposures seen in the adult population. It was determined that dosing on surface area (m^2) reduced the variability observed than on a weight (mg/kg) basis.

Conclusion: This study was stopped prematurely when it was determined that the 23 mg/kg bid dosing regimen produced the desired exposure observed in the adult renal transplant patients receiving 1 gm bid. It was hypothesized that dosing on surface area basis was better than on a weight basis. 23 mg/kg was extrapolated to be 600 mg/ m^2 .

Drug Interactions: Potential drug interactions applicable to the administration of Cellcept to pediatric renal transplant population are similar to those described previously in the adult transplant population.

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Summary of MPA AUC₀₋₁₂ with 95% CI by Age Subgroup

Table 12

Dose Normalized AUC₀₋₁₂

Day 7

	>= 3 months to < 6 years	>= 6 years to < 12 years	>= 12 years to 18 years	< 2 years
Mean	27.4	33.2	26.3	22.5
Std.Dev.	9.54	12.1	9.14	6.66
CV	34.8	36.3	34.8	29.6
Min	15.7	13.6	14.8	16.8
Max	51.9	53.3	52.8	32.0
n	17	16	20	6
95% Confidence Interval	[22.8, 31.9]	[27.3, 39.2]	[22.3, 30.3]	[17.2, 27.8]

Month 3

	>= 3 months to < 6 years	>= 6 years to < 12 years	>= 12 years to 18 years	< 2 years
Mean	49.7	61.9	53.6	47.4
Std.Dev.	18.2	19.6	20.3	14.7
CV	36.6	31.6	37.9	31.0
Min	20.5	34.2	25.6	34.3
Max	95.9	95.0	106.	67.1
n	15	14	16	4
95% Confidence Interval	[40.5, 58.9]	[51.6, 72.1]	[43.7, 63.5]	[33.0, 61.8]

Month 9

	>= 3 months to < 6 years	>= 6 years to < 12 years	>= 12 years to 18 years	< 2 years
Mean	61.0	66.8	56.7	55.8
Std.Dev.	10.7	21.2	14.0	11.6
CV	17.6	31.7	24.6	20.9
Min	41.7	39.4	29.4	41.7
Max	79.4	105.	80.0	67.0
n	12	11	14	4
95% Confidence Interval	[54.9, 67.0]	[54.3, 79.3]	[49.4, 64.0]	[44.4, 67.2]

Note: Dose Normalized AUC₀₋₁₂ was dose adjusted to 600 mg/m²

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Table 13

**[CI_PED_ADULT.PDF] Early Post-Transplant
MPA Computed Parameter Confidence Interval Summary
Comparison of Group (A) vs Group (B)**

Untransformed Scale

Computed Parameter	Ratio (A/B)	90% Confidence		95% Confidence	
		Lower Limit	Upper Limit	Lower Limit	Upper Limit
AUC 0-12	102.0%	91.1%	112.9%	89.0%	115.0%
Dose Adj. AUC 0-12	105.7%	94.7%	116.8%	92.5%	118.9%
Cmax	106.2%	89.5%	127.0%	85.8%	130.6%
Dose Adj. Cmax	112.7%	93.7%	131.7%	90.1%	135.4%

Log Transformed Scale

Computed Parameter	Ratio (A/B)	90% Confidence		95% Confidence	
		Lower Limit	Upper Limit	Lower Limit	Upper Limit
AUC 0-12	107.1%	96.1%	119.4%	94.1%	122.0%
Dose Adj. AUC 0-12	106.2%	97.2%	120.4%	95.2%	122.9%
Cmax	110.4%	92.5%	131.7%	89.4%	136.3%
Dose Adj. Cmax	114.1%	95.6%	136.3%	92.3%	141.1%

Groups:

A = MMF Oral BID 600 mg/m² Day 7 in Pediatric Population

B = MMF Oral BID 1 g Day 3, 7, and 11 in Adult Population

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