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APPLICATION NUMBER:

50-722/S-007

50-723/S-004

50-759/S-005

MEDICAL REVIEW

**Medical Officer Review of NDA 50-722, SE5-007:
mycophenolate mofetil (CellCept ®)**

Date Submitted: 18-FEB-2000
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Applicant: Roche Pharmaceuticals
Drug: Proprietary name - CellCept ®
Generic name - (mycophenolate mofetil, MMF)

Chemical name-

2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)- 4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$.

Molecular formula - $C_{23}H_{31}NO_7$

Molecular weight - 433.50.

Molecular structure - (see label)

Drug Class: antibiotic
Formulation: Oral Suspension (oral solution, 200 mg/ml)
Route of administration: Oral

Related NDAs: 50-722: 250 mg capsules
50-723: 500 mg tablets
50-758: 500 mg injectable
50-759: oral suspension 200 mg/mL

Related INDs:

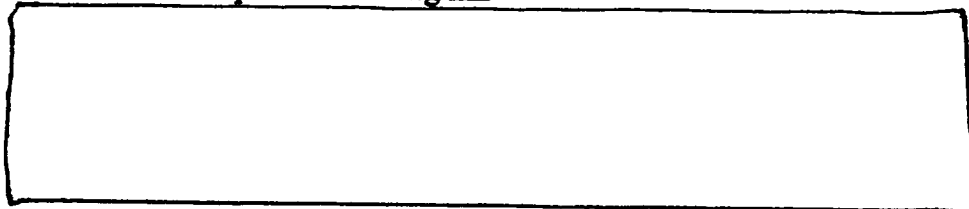


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EXECUTIVE SUMMARY

This supplemental NDA was submitted to support the use of CellCept® for prophylaxis of organ rejection in pediatric patients receiving renal transplants in combination with cyclosporine and steroids. Pursuant to 21CFR201.57 (f)(9)(iv), the label revision is based on adequate and well-controlled studies in adult renal transplantation (NDA 50-722), with supporting data from pediatric studies.

To evaluate the pharmacokinetics, safety and efficacy of CellCept® in pediatric patients, Roche conducted one pivotal, single-arm, open-label study (MYCS2675) in 100 pediatric renal allograft recipients ranging in age from 3 months to 18 years. Results have been compared to data from the primary controlled adult renal transplant studies previously conducted. Prior to starting the pediatric program, Roche proposed and obtained FDA agreement on this strategy (March 1997).

The applicant provided the following rationale supporting the assumption that rejection in adult and pediatric patients is similar and that CellCept® would be expected to prevent rejection by similar mechanisms in adult and pediatric patients.

"The mechanism of action of CellCept® in the prevention of renal transplant rejection in both adult and pediatric patients is based on the metabolism of CellCept® to its active moiety, mycophenolic acid (MPA). MPA selectively and reversibly inhibits inosine monophosphate dehydrogenase (IMPDH), which is the committed step in *de novo* guanosine nucleotide biosynthesis. There are no data to suggest that IMPDH differs qualitatively or quantitatively in the adult and pediatric populations. As the inhibition of IMPDH (as with MPA) results in clinical immunosuppression, it is assumed that differences in IMPDH function and levels between adults and children would be manifested clinically as immunodeficiency. Further indirect evidence that abnormalities in IMPDH expression result in clinically evident disease is supported by the observation that pediatric patients, who had a 30-fold increase in the activity of IMPDH in red blood cells, manifested neurologic disease (spastic diplegia) as well as an immunodeficiency state (recurrent infections). In addition, elevated IMPDH levels in nucleated cells are associated with human neoplasia, including leukemias. Therefore, both adult and pediatric renal transplant recipients who are otherwise immunologically competent at the time of transplantation are assumed to have the same IMPDH level and function."

The efficacy and safety results suggest similarities between adult and pediatric patients for the prevention of renal allograft rejection. The rate of biopsy proven rejection (BPR) observed at 6 months for pediatric renal transplant recipients (on-study and post-termination) in study MYCS2675 of 19% was similar to the rate of 20% observed in each of the two adult pivotal renal transplant studies MYC1866 and MYC023. The 6-month rates of BPR or presumptive rejection observed in pediatric patients (on-study and post-termination) in MYCS2675 (22%) were also similar to the corresponding rates in the adult studies MYC1866 and MYC023 (26% and 32%, respectively). It should be noted that the rejection rates reported in the adult trials were for on-study events only;

therefore, the occurrence of the first acute rejection in those patients who terminated prematurely was not captured. As a consequence, the observed adult 6-month acute rejection rates are likely to be underestimates. This suggests that the pediatric acute rejection rate is favorable.

In the pivotal pediatric study MYCS2675, excluding death with a functioning graft, five graft losses have been observed during the first 12 months posttransplant. The reasons for graft loss were technical complications in three cases and graft rejection in two cases.

Two deaths were observed during the first year of follow-up in study MYCS2675: one due to pulmonary embolism and the other to acute hemorrhagic pancreatitis. Neither death was considered related to MMF treatment. Overall, the 1-year pediatric graft survival rate (including graft loss or death) of 93% is similar to the observed rates of 88–92% in adult MMF-treated patients.

The safety of MMF in children at the recommended dose of 600 mg/m^2 bid is based upon a 140 patient database. Qualitatively, the safety profile of MMF in pediatric renal transplant patients was similar to that observed in adult renal transplant patients. The youngest children experienced increased episodes of certain Aes (adverse events) including diarrhea, anemia, leukopenia and sepsis. However, these events either resolved spontaneously or with MMF dose modification. Furthermore, these events infrequently led to study discontinuation, had no long-term clinical sequelae and did not lead to death.

Two cases of malignancy occurred in the pediatric group, both classified as lymphoma/lymphoproliferative disease (LPD). One case (study MYCS2675) occurred within 1 year (280 days) after starting MMF treatment; the other (study MYCS2190) occurred more than 3 years after starting MMF treatment. The resulting proportion of lymphoma/LPD in the pediatric group after 1 year ($1/140=0.7\%$) is very similar to that observed in the corresponding adult MMF-treated renal transplant population ($2/336=0.6\%$). To date, no other types of malignancies have been reported in pediatric patients.

Based upon review of data submitted it appears that the safety and efficacy of CellCept in pediatric renal transplant recipients is similar to that of adult patients.

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1.0 Background

In the U.S. from 1993 to 1997, 6% of all kidney transplants were performed in children under 18 years of age. Of these, about 19% of the recipients were younger than 6 years, 21% were 6-10 years, and 60% were 11-17 years of age.

The risk factors for poor graft survival apply to both adult and pediatric populations: cadaver donor source, black race, previous transplant, occurrence of acute rejection in the early posttransplant period, and increased HLA mismatching. Both young recipient age (< 2 years) and young donor age (< 6 years) also adversely influence graft survival. Graft and patient survival rates improve when kidneys from living-related donors are used. The 1-year graft survival rates in 1997 for recipients of living-related donor kidneys were 89.5% for patients under 5 years and 94.6% for ages 18 - 34 years. In the recent era, overall 1-year graft survival rates in children have improved (85-94%) and are similar to those observed in adults (83-94%).

Despite the improvement in early graft survival rates, poor long-term survival as a result of chronic rejection continues to be a significant problem in children, as well as adults. The most common causes of graft loss in pediatric transplant recipients are chronic rejection (28% of graft loss), acute rejection (18%), vascular thrombosis (13%), and patient death (11%). As in adults, the main risk factor for the development of chronic rejection in children is the occurrence of acute rejection. It is reported that acute rejection develops in 40-70% of pediatric renal transplant recipients, the majority occurring within the first 3 months posttransplant. Thus, rejection (chronic and acute) directly impacts graft loss.

CellCept (mycophenolate mofetil, MMF) is approved and marketed for use in adults as an immunosuppressant for concomitant use with cyclosporine and corticosteroids to prevent rejection following renal or cardiac transplantation. MYCS2675 is the second of two pediatric studies performed to date to evaluate the use of MMF in the prevention of acute rejection in pediatric renal allograft recipients. In a previous study and its safety extension (IID/MYC2190/USA and MYCS2190v2), MMF was examined for safety, tolerability, and prevention of acute rejection in this population. That pilot study provided the first characterization of the pharmacokinetics of MMF and its main metabolite (mycophenolic acid glucuronide, MPAG) in pediatric renal transplant recipients, providing the basis for the dosing used in study MYCS2675.

In vivo, MMF is hydrolyzed to MPA (mycophenolic acid), the active moiety. MPA is a potent and specific inhibitor of de novo purine synthesis that acts by uncompetitive inhibition of inosine monophosphate dehydrogenase, thereby blocking the proliferation of both T- and B-lymphocytes. MPA is metabolized further to form a glucuronide conjugate (mycophenolic acid glucuronide, MPAG), which is pharmacologically inactive.

The pediatric clinical program was designed to assess the safety, tolerability and pharmacokinetics of MMF, and to describe the efficacy of MMF, for the prevention of acute renal allograft rejection in pediatric recipients. The pediatric program consisted of (1) a pilot study, MYC2190 and its extension MYCS2190V2, and (2) a pivotal study, MYCS2675. A total of 140 pediatric patients (defined as an individual between three

months and 18 years of age, inclusive) participated in one of these two phases of the pediatric clinical program.

An additional 21 pediatric patients, of ages 8 to 18 years, received MMF in studies primarily designed for adults. (1) Fifteen of these patients had received renal transplants and received MMF for the treatment of refractory rejection (studies MYCS1868 and ICM 1812). (2) Two cardiac and two hepatic transplant recipients also received MMF for the treatment of refractory rejection (study ICM 1812). (3) Two hepatic transplant recipients received MMF for the prevention of hepatic allograft rejection (study MYCS2646). Thus, a total of 161 pediatric patients received MMF.

The assessment of the safety of MMF in the pediatric population is based on a comparison of the pediatric safety data to that of the adult population. This comparison is warranted because the course of end stage renal disease (ESRD) and the mechanism of action and metabolism of MMF are sufficiently similar in both the pediatric and adult populations. Adult safety data are derived from 336 renal transplant patients from studies MYC1866 and MYC023, the pivotal controlled adult studies in renal transplantation.

FINANCIAL DISCLOSURE:

The applicant reported that no investigator participating in the safety study had a significant number of subjects which would bias the outcome of the pivotal study. Upon review of the pivotal study, there were 16 investigators participating in the study at 15 sites. One investigator had enrolled 23 % of the subjects, and most have enrolled less than 10%. Therefore, financial information is not required for investigators participating in this study.

SITE INVESTIGATIONS:

No individual site investigations were undertaken in review of this study. Previously, Roche/Syntex sites had been investigated and were found to be acceptable. The conduct of studies performed for CellCept have been of excellent quality. In addition, none of the sites enrolled large numbers of patients. There were no indications from review of this submission that site investigation was warranted.

2.0 Study Review (MYCS2675)

Study MYCS 2675 is an open-label, safety, tolerance, and pharmacokinetic study of oral mycophenolate mofetil suspension in the prophylaxis of rejection in pediatric renal allograft recipients.

The objective of this study was 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.

A total of 100 first or second renal allograft recipients were enrolled into one of three defined age groups: 33 patients aged 3 months to < 6 years, 34 patients aged 6 to < 12 years, and 33 patients aged 12 to 18 years (inclusive). Seventeen, 17 and 21 patients from these respective age groups participated in the PK portion of the study.

Patients received MMF oral suspension 600 mg/m² bid, up to 1 g bid. After study month 9, if certain protocol-defined criteria were met, patients were allowed to switch to capsule formulation if desired.

Efficacy parameters included prophylaxis of acute rejection at 6 months; patient and graft survival at 6 and 12 months; and immunosuppressive medications administered for treatment of rejection at 6 months.

Medical Officer Comment:

The development and conduct of this study occurred prior to current FDA guidance regarding age groupings of pediatric patients to be studied. Therefore it was recommended that in addition to the planned analysis by the protocol specified age groups, the applicant perform analyses for patients in the population of patients 2 years of age or younger.

Efficacy parameters are similar to those used to assess the activity of CellCept in the adult renal transplant populations. However, the amount of information collected regarding rejection for any patient treated with CellCept during the first 6 months is more complete for the pediatric patients. In addition, requirements for reporting of any adverse event regardless of potential relationship to CellCept were made after the adult renal transplant indication was approved. Thus, for both the rejection endpoint and adverse event rates, the reported rates in the adult portion of the label may be underestimates. This is important to consider when any comparisons of the data are being made between adult and pediatric populations.

Pharmacokinetics Sub-Study:

For 55 patients participating in the PK portion of the study, computed MPA and MPAG parameters were obtained from plasma concentrations of collected over 12 hours on day 7, month 3 and month 9. (For additional details please refer to Biopharmaceutics Review, Dr. Kofi Kumi).

2.1 Demographics

Summary of Key Baseline Characteristics for MYCS2675 (All Patients Enrolled)

	MMF Treatment Group (600mg/m ² bid)			
	< 6 y n = 33	6 – < 12 y n = 34	12 – 18 y n = 33	TOTAL n = 100
Previous Transplant				
No	30 (91%)	30 (88%)	27 (82%)	87 (87%)
Yes	3 (9%)	4 (12%)	6 (18%)	13 (13%)
Type of Donor				
Cadaver	6 (18%)	22 (65%)	16 (48%)	44 (44%)
Living-Related	26 (79%)	12 (35%)	16 (48%)	54 (54%)
Living-Unrelated	1 (3%)	0	1 (3%)	2 (2%)

CMV Status (Donor/Recipient)				
+/+	14 (42%)	8 (26%)	8 (24%)	30 (31%)
+/+	8 (24%)	5 (16%)	14 (42%)	27 (28%)
-/+	1 (3%)	6 (19%)	2 (6%)	9 (9%)
-/-	10 (30%)	12 (39%)	9 (27%)	31 (32%)
Not Done	0	3	0	3
EBV status				
Positive	8 (25%)	20 (59%)	22 (71%)	50 (52%)
Negative	24 (75%)	14 (41%)	9 (29%)	47 (48%)
Missing	1	0	2	3
HLA A+B+DR # of Mismatches				
0	1 (3%)	0	1 (3%)	2 (2%)
1	2 (6%)	0	4 (12%)	6 (6%)
2	6 (18%)	6 (18%)	7 (21%)	19 (19%)
3	16 (48%)	18 (55%)	12 (36%)	46 (46%)
4	6 (18%)	5 (15%)	6 (18%)	17 (17%)
5	2 (6%)	4 (12%)	2 (6%)	8 (8%)
6	0	0	1 (3%)	1 (1%)
# missing	0	1	0	1

(Reference Vol. 9, p. 47)

Of the eight patients under two years of age, four had a congenital abnormality, and four listed "other" as their reason for loss of the native kidney. Specific causes for these latter four were congenital nephrotic syndrome, HUS, Drash syndrome, and cortical necrosis. All eight patients received their first renal transplant, seven of which were from LRD (one cadaveric).

The percentage of females enrolled into the study was 32%. The racial breakdown was as follows: caucasian, 72%; black, 11%; asian, 4%; hispanic, 7%; other, 3%.

The following comments regarding race and gender are quoted from the applicant submission.

"The gender mix enrolled in the overall study population and in the PK profiling was consistent with the pediatric population in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) registry, which is composed of 40% female and 60% male patients. The gender mix also corresponds to the male:female ratio of all individuals (including adults) with end-stage renal disease reported in the European Dialysis and Transplantation Association (EDTA) database."

"The racial subgroup percentages generally reflected those of the pediatric renal transplant population in the United States (approximately 72.6% white, 20.7% black, 2.9% Asian, 1.3% Native American, and 2.1% "other"). It is difficult to describe the overall racial distribution in the EU; some countries are multiracial, whereas in the UK, for example, there are large minority populations of Indian, Caribbean, and African origin."

"The proportion of blacks enrolled in MYCS2675 (11/100, 11%) was greater than that for the combined African/Caribbean population with end-stage renal disease in the United Kingdom (7.2%), but was lower than the proportion of black patients in the general U.S. pediatric transplant population. However, all black patients in the study were enrolled only at U.S. sites. In the context of all U.S. patients enrolled, the proportion of black patients (11/53, 20.8%) reflected that of the black pediatric renal transplant population in the United States."

Medical Officer Comment:

In general the mix of patients by race and gender is acceptable.

2.2 Dosing

The mean oral MMF dose received for the initial 12 months of the study was balanced between the three age groups: 524.25 mg/m² bid, 551.4 mg/m² bid, and 542.35 mg/m² bid for the < 6 year, 6 - < 12 year, 12 - 18 year groups, respectively. The mean MMF dose for all patients participating in the PK analysis (shown for each sampling time), and for each age group, gender, and racial subgroup, were similar to the mean MMF dose calculated for the overall study population. The mean (and range) of doses for all PK patients at day 7, month 3 and month 9 was 581 mg/m² bid [redacted] 544 mg/m² bid [redacted] and 533 mg/m² [redacted] bid, respectively.

Medical Officer Comment:

The mean dose was comparable across age groups. In general the mean dose is slightly under the target dose, as was the case in the adult renal transplant studies.

2.3 Antibody Induction

Seventy-three of the 100 patients enrolled were given antibody induction therapy; administration was uniform across age groups. The majority of these patients received [redacted] particularly those in the two youngest groups. Other types of induction therapy included [redacted] or a combination of these medications. Two patients received two treatments: one patient in the youngest group received [redacted] for eight days, then [redacted] for 5 days, and one patient received [redacted] for 5 days followed by [redacted] for one day.

All eight patients in the < 2 year subgroup received [redacted] for induction therapy.

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(Reference Vol 9, p 52, table 9)

Medical Officer Comment:

It should be noted that the effect of [] upon the background therapy of CellCept, steroids and cyclosporine has not been studied. In this study it is only used in 5 patients for induction therapy. In addition, in the adult renal studies, a lower amount of induction therapy was used in general. This should be kept in mind with making comparisons with adult patients.

2.4 Extent of Exposure to MMF and Duration of Treatment

Eighty-one of 100 patients (81%) received study drug for at least six months, and 71 (71%) patients were on study drug for a minimum of 1 year (22 patients were included within the period of 351 to 365 days on treatment).

Medical Officer Comment:

This proportion of patients remaining on study through one year was similar to that in the adult renal transplantation studies.

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2.5 Study Results

2.5.1 Efficacy

2.5.1.1 Biopsy Proven Rejection (6 months)

The applicant reported the rates of rejection in the following tables.

Summary of First Biopsy Proven Rejection or Presumptive Rejection During First Six Months Posttransplant (Pediatric Criteria)

Biopsy Proven Rejection/ Presumptive BPR	< 6 y (n = 33)	6 - < 12 y (n = 34)	12 - 18 y (n = 33)	TOTAL (n = 100)
Borderline	3 (9.1%) ^A	1 (2.9%)	3 (9.1%) ^B	7 (7.0%) ^A
Grade I	2 (6.1%)	7 (20.6%)	2 (6.1%)	11 (11.0%)
Grade IIA	1 (3.0%)	1 (2.9%)	2 (6.1%)	4 (4.0%)
Grade IIB	0	0	2 (6.1%)	2 (2.0%)
Grade III	0	0	0	0
Total BPR	6 (18.2%)	9 (26.5%)	9 (27.3%)	24 (24.0%)
BPR or Presumptive Rejection	7 (21.2%)	9 (26.5%)	9 (27.3%)	25 (25.0%)

Note: Results of intent-to-treat analysis using local site biopsy readings.

^A One patient was treated for presumptive rejection (not counted here as presumptive), and later experienced borderline rejection.

^B Two patients had a second rejection episode with a Banff score of Grade III; these are not recorded in the Grade III events in this table.

(Reference Vol 9, p 73)

Summary of First Biopsy Proven Rejection During First Six Months Posttransplant (Adult Criteria)

BPR	< 6 y (n = 33)	6 - < 12 y (n = 34)	12 - 18 y (n = 33)	TOTAL (n = 100)
Grade I	2 (6.1%)	7 (20.6%)	2 (6.1%)	11 (11.0%)
Grade IIA	1 (3.0%)	1 (2.9%)	2 (6.1%)	4 (4.0%)
Grade IIB	0	0	2 (6.1%)	2 (2.0%)
Grade III	0	0	2 (6.1%)	2 (2.0%)
Total BPR	3 (9.1%)	8 (23.5%)	8 (24.2%)	19 (19.0%)
BPR or Presumptive Rejection	5 (15.2%)	8 (23.5%)	9 (27.3%)	22 (22%)

Note: table presents data from initial 6 months on study using intent to treat analysis of local site biopsy readings.

(Reference: vol 9, p 73)

Biopsies were collected through the first six months posttransplant on all patients who experienced a rejection episode. All biopsies with a Banff score of Grade I, IIA, IIB, III, and borderline rejection, as assessed by the local site pathologist, were included as BPR (pediatric criteria); a central reader was used to confirm biopsy results as read by the local pathologist. Data from the same local biopsy readings were also summarized using adult criteria. All efficacy data in this report are based on results from the local reader. Note that while the adult criteria exclude borderline rejection from the BPR category, an episode of borderline rejection would be included within the category of presumptive rejection if a patient received immunosuppressive treatment for borderline rejection.

Using the pediatric criteria for BPR assessment, the number of patients experiencing BPR or presumptive rejection was similar across the age groups. A comparison between the pediatric and adult criteria for the number of patients experiencing BPR or presumptive rejection showed a discrepancy of two and one patients in the < 6 year and 6 - < 12 year age groups, respectively. The observed discrepancy is due to these three episodes of borderline rejection, which were not treated with immunosuppressive medication.

Four additional BPR episodes were reported in the period between 6 months posttransplant and the cutoff date for this interim report (two patients in each of the two older age groups.) An additional six patients were treated with a full course of immunosuppressive medication for rejection (one, two, and three patients in the youngest to oldest groups, respectively).

Medical Officer Comment:

The age group classification reported by the applicant differs due to the fact that these studies were planned and initiated prior to the FDA pediatric guidance regarding pediatric age groups. Because of our interest in patients which were studied in the age group < 2 years, additional information was requested from the applicant regarding the specific out comes of these patients. For purposes of this discussion only 2 of the 8 patients 2 years of age or younger had biopsy proven rejection in the first 6 months. Neither of these 2 patients had graft loss or death at 12 months.

The rates of biopsy proven rejection in the adult studies ranged between 17 to 20%. These may be slightly lower estimates when compared to the pediatric group due to the more complete follow up regarding renal biopsies in this pediatric study. The adult studies had slightly different data collection requirements (see description in the label). While the pediatric population reported here represents a smaller pool of patients from which to derive a biopsy proven rejection rate, it appears to be similar to the adult rate when adult criteria are used (19%). It is slightly higher when the borderline cases are included.

While biopsy proven rejection at six months was utilized extensively in the past as a measure of activity of the immunosuppressive regimen, today more attention is being paid to the 12 month death and graft loss endpoint, as well as the renal function at 12 months. (See below for further discussion)

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2.5.1.2 Twelve month graft loss

The following is a summary of the twelve month graft loss and death.

Summary of Patient Graft Loss in MYCS2676

Cause of Graft Loss Patient No.	Age Group	Days Post-transplant	Technical Complication/ Local Biopsy Banff Score	Outcome
53363	6 - < 12 y	2	Thrombosis of Graft	Nephrectomy
53303	12 - 18 y	46	Renal Vein Thrombosis	Nephrectomy
53017	12 - 18 y	4	Renal Artery and Renal Vein Thrombosis	Nephrectomy
Graft Rejection:				
53212	12 - 18 y	8	Grade IIB (d8 post-tx)	Nephrectomy
53093	12 - 18 y	263	Borderline (d8 post-tx); Grade III (d109 post-tx); Grade IIA (d234 post-tx)	Dialysis Dependence A

A

Defined as > 42 consecutive days on dialysis.

(Reference: vol 9, p 77)

Medical Officer Comment:

Seven patients lost their grafts during a minimum follow-up of 12 months, including two patients who died with a functioning graft, for a patient and graft survival rate of 93%. This compares favorably with the adult 12 month graft loss and death rates (8.5-11.7% for the 2 gram dose) (see current label, appendix A).

2.5.1.3 Renal Function

Calculated creatinine clearance and serum creatinine (mM/L) were summarized by age group at days 7, 14, 28, and 56, and months 3 - 6, 9, and 12 (See tables below). Mean creatinine clearance was higher for the two youngest groups through day 14, and creatinine levels for the 6 - < 12 year group generally remained slightly higher, relative to the other two age groups. Mean serum creatinine levels decreased from day 7 to month 3 for all age groups, as expected, after which mean values generally remained stable through the sixth month assessment period.

Summary of Creatinine Clearance (ml/min)

	MMF SUSPENSION 600 mg/m ² bid			
	< 6 y	6 - < 12 y	12 - 18 y	TOTAL

DAY 7				
Patients in study	32	33	31	96
Patients with missing data	0	1	0	1
Mean	70.7	79.0	56.3	68.8
SD	37.5	49.3	31.3	40.3
Median	67.2	65.3	52.3	64.3
Range				
MONTH 3				
Patients in study	32	32	25	89
Patients with missing data	0	0	0	0
Mean	64.8	74.1	63.3	67.7
SD	23.3	32.0	19.6	26.1
Median	63.1	70.7	56.6	63.6

Range				
MONTH 6				
Patients in study	31	30	21	82
Patients with missing data	1	0	0	1
Mean	63.8	70.9	64.5	66.6
SD	37.5	23.8	15.9	28.1
Median	57.5	68.8	64.3	63.6
Range				
MONTH 9				
Patients in study	30	28	20	78
Patients with missing data	0	0	0	0
Mean	64.2	76.7	68.1	69.7
SD	23.4	30.0	30.5	28.0
Median	62.3	70.7	68.3	67.0
Range				
MONTH 12				
Patients in study	28	27	18	73
Patients with missing data	0	0	0	0
Mean	63.2	70.4	72.4	68.1
SD	24.5	22.2	22.9	23.3
Median	56.0	70.7	68.3	66.9
Range				

Note: Creatinine clearance (ml/min/1.73m²) was calculated using the following formula, specifically developed for pediatric patients : $[(0.035 \times \text{Age [y]}) + 0.236] \times 100 / \text{serum creatinine [mg/dL]}$

(Reference: Vol 9, p 78)

Summary of Patient Serum Creatinine (mg/dL)

	MCF SUSPENSION 600 mg/m ² bid			
	< 6 y	6 - < 12 y	12 - 18 y	TOTAL
DAY 7				
Patients In Study	32	33	31	96
Patients With Missing Data	0	1	0	1
Mean	0.96	1.10	1.94	1.33
SD	1.42	1.26	1.39	1.41
Median	0.40	0.88	1.60	0.88
Range				
MONTH 3				
Patients In Study	32	32	25	89
Patients With Missing Data	0	0	0	0
Mean	0.59	0.86	1.29	0.88
SD	0.24	0.38	0.41	0.44
Median	0.57	0.83	1.30	0.80
Range				
MONTH 6				
Patients In Study	31	30	21	82
Patients With Missing Data	1	0	0	1
Mean	0.66	0.87	1.26	0.89
SD	0.34	0.34	0.36	0.41
Median	0.57	0.83	1.20	0.80
Range				

MONTH 9				
Patients In Study	30	28	20	78
Patients With Missing Data	0	0	0	0
Mean	0.66	0.84	1.89	1.04
SD	0.30	0.40	2.62	1.43
Median	0.61	0.70	1.15	0.71
Range				
MONTH 12				
Patients In Study	28	27	18	73
Patients With Missing Data	0	0	0	0
Mean	0.68	0.86	1.20	0.87
SD	0.31	0.31	0.45	0.40
Median	0.60	0.80	1.10	0.80
Range				

Patient No. 53093 was on dialysis due to graft rejection at this time point, with a serum creatinine value of 12.50 mg/dL (termination visit, July 31, 1998).
(Reference: Vol 9, p.79)

Medical Officer Comment:

The renal functions represented by the creatinine and creatinine clearances are acceptable. There is no pediatric control group with which to compare these data.

2.5.2 Safety Results (MYCS3675)

2.5.2.1 Adverse Events (All Cause)

All patients experienced at least one adverse event.

Summary of Safety Results

Safety Parameter	Number of Patients n = 100	% of Patients
Overall incidence of adverse events	100	100.0
Deaths	2	2.0
Malignancies	1	1.0
Patients withdrawn for adverse events	10	10.0
Patients with medically serious adverse events	16	16.0
Patients with adverse events possibly/probably related to MMF	81	81.0
Patients with severe adverse events	54	54.0
Adverse events resulting in dose interruption or dose reductions	49	49.0
Opportunistic infections	48	48.0

(Reference: vol 9, p 4)

AEs were reported in similar numbers for the three defined pediatric age groups. Certain types of AEs were observed more frequently in the two youngest groups (< 6 year and 6

- < 12 year). These included leukopenia, diarrhea, and anemia. (See appendix B for listing of adverse events occurring in ≥ 10 of patients).

All patients experienced at least one adverse event through the cutoff date (September 20, 1999). The proportion of patients reporting AEs across the age groups was similar for the large majority of events reported. However, diarrhea and leukopenia occurred more frequently in the two youngest groups, while vomiting, anemia, and sepsis were more frequent in the < 6 year group. Conversely, events involving nausea and constipation were more frequent in the oldest patients: 4 (12.1%), 11 (32.4%), 15 (45.5%) for nausea; and 7 (21.2%), 5 (14.7%), and 14 (42.4%) for constipation in the youngest to oldest age groups, respectively. When nausea and vomiting are considered together as one entity for gastric distress, the number of patients experiencing one of these AEs was distributed equally across the age groups (27, 26, and 27 respectively). Combining events for diarrhea and constipation indicates that the number of patients who experienced digestive disturbances was fairly similar across the age groups (38, 28 and 24 for the youngest to oldest groups, respectively).

Sepsis due to bacteremia predominated in the youngest group, and accounted for the larger number of AEs for sepsis in that age group, affecting 10, 4, and 2 patients in the < 6, 6 - < 12, and 12 - 18 year groups, respectively. Sepsis due to CMV infection was fairly similar across the age groups (6, 9, and 6 patients for the youngest to oldest groups, respectively). (Note that some patients reported both bacteremia and CMV as causes for sepsis.)

Summary of Selected AEs Reported More Frequently in the Youngest Groups

AE	< 2 y ^A	Age Group < 6 y (n = 33)	6 - < 12 y (n = 34)	12 - 18 y (n = 33)	TOTAL (n = 100)
Diarrhea	8 (100%)	29 (87.9%)	23 (67.6%)	10 (30.3%)	62 (62%)
Vomiting	7 (87.5%)	23 (69.7%)	15 (44.1%)	12 (36.4%)	50 (50%)
Anemia	5 (62.5%)	17 (51.5%)	11 (32.4%)	9 (27.3%)	37 (37%)
Sepsis	4 (50%)	16 (48.5%)	11 (32.4%)	8 (24.2%)	35 (35%)
Leukopenia	2 (25%)	10 (30.3%)	10 (29.4%)	4 (12.1%)	24 (24%)

^A The < 2 year group is a subset of the < 6 year group.

(Reference: Vol 9 , p 54)

The proportion of patients experiencing leukopenia and sepsis in the < 2 year subgroup was similar to those for the < 6 year group, with a higher incidence of diarrhea, vomiting, and anemia in the < 2 year patients

Medical Officer Comment:

The types of events described above were similar to those seen in the adult renal transplant population. Some of the gastrointestinal events seemed to be more frequent in the youngest patients, these patients may have more frequent gastrointestinal events in general. There is no comparative pediatric group from which to make further comparisons. Further comparisons with the adult population will be made below.

2.5.2.2 Withdrawal due to Adverse Events

Ten patients (10%) withdrew from the study due to adverse events; six of these withdrawals were considered by the investigator to be possibly or probably related to study drug.

Patients Prematurely Withdrawn from the Study Due to Adverse Events

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(Reference: vol 9, p 42)

Medical Officer Comment:

The types of adverse events for which investigators withdrew patients from study are consistent with the events seen in adult renal transplant patients. Renal vein thrombosis and artery thrombosis were most likely not related to study drugs.

2.5.2.3 Severe Adverse Events

Through the first year of the study, 54% of patients reported at least one severe adverse event (an AE assigned a toxicity grade of 3, 4, or fatal) and/or one or more severe OIs, as graded by the investigator. The occurrence of most severe AEs was low, and was evenly distributed across the age groups. Severe anemia and leukopenia were reported in greater proportion for the youngest age group. However, the number of patients reporting these events was small.

Three patients reported severe diarrhea (all in the < 6 year group), and one (No. 53276) withdrew prematurely due to this AE:

- Patient No. 53181 experienced severe diarrhea for 3 days, and MMF dose was reduced; the event recurred and was then re-classified as not related to study drug;
- Patient No. 53423 experienced diarrhea for four days, which was not considered related to study drug, and there was no recurrence;
- Patient 53276 had severe diarrhea for four days; MMF was interrupted and the patient was hospitalized; the next day diarrhea recurred and the patient was withdrawn from the study.

Summary for Severe Adverse Events of Anemia, Leukopenia and Diarrhea

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(Reference: vol 9, p 55)

Four patients under two years of age reported a total of 10 severe AEs. Two patients (2/8, 25%) experienced severe anemia; one of these patients, Patient No. 53122 (withdrawn due to EBV infection), reported a total of five severe AEs, including severe leukopenia and thrombocytopenia.

Medical Officer Comment:

The events reported above are similar in type as those seen within the adult transplant populations.

2.5.2.4 Serious Adverse Events

The following table summarized serious adverse events.

MSAE ^a	< 6 y (n = 33)	6 - < 12 y (n = 34)	12 - 18 y (n = 33)	Total (n = 100)
Malignancy	1 (3 %)	0	0	1 (1%)
Severe Thrombocytopenia	0	0	1 (3.0%)	1 (1.0%)
Death	0	1 (2.9%)	1 (3.0%)	2 (2.0%)
Severe Neutropenia	2 (6.1%)	1 (2.9%)	0	3 (3.0%)
GI Bleeding Requiring Hospitalization	0	1 (2.9%)	2 (6.1%)	3 (3.0%)
Premature withdrawal due to AE intercurrent illness, or lab abnormality	3 (9.1%)	3 (8.8%)	4 (12.1%)	10 (10%)

^a Counts only patients on study drug, except for malignancy and death, which include patients withdrawn from study
(Reference: vol 1, p. 52)

Medical Officer Comment:

Narratives of these events were reviewed. The medical officer is in agreement with the data represented above. Further exploration of patients listed to have had any gastrointestinal bleeding revealed 8 patients. Five of these patients had mild to moderate episodes. All but one were noted to be probably not related by the investigators. Many occurred in the early perioperative period.

2.5.2.4 Deaths

Two patients died while on study: one due to acute hemorrhagic pancreatitis, and one to pulmonary embolism. Neither event was considered by the investigator to be related to study drug.

(Reference: vol 9, p. 52)

Medical Officer Comment:

Case Report Forms and Case Narratives presented by the applicant were reviewed. It appears that neither of these deaths was drug related.

2.5.2.5 Malignancies

One malignancy was reported in study MYCS2675, for an overall malignancy rate of 1% (1/100) at one year posttransplant. This patient was EBV positive at baseline, received antibody induction treatment () and experienced a BPR of Grade 2A at 146 days posttransplant, which was treated with corticosteroids. He was diagnosed with posttransplant lymphoproliferative disease (PTLD) (lesions on liver and spleen), considered by the investigator as probably related to study drug. No treatment was administered other than reduced immunosuppression: MMF and cyclosporine were discontinued, and corticosteroid dosage was reduced. The patient was withdrawn after 280 days of study participation. One hundred thirty days after study drug discontinuation, the patient showed marked improvement.

Medical Officer Comment:

The rate of malignancy is similar to that seen in adult patients. There is insufficient data available to draw conclusions regarding the degree of immunosuppression caused by the use of this antibody induction treatment and mycophenonlate mofetil. This combination is not approved by the FDA.

2.5.2.6 Opportunistic infections

OIs occurred in 48 patients (48%). All age groups reported events for CMV viremia/syndrome, candida, herpes simplex, and herpes zoster. Events were reported in similar proportions for each age group with the exception of candida mucocutaneous, which was experienced by the < 6 year group in greater numbers relative to the older two groups (21.2%, 5.9%, 3.0% for the youngest to oldest groups, respectively).

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Summary of Patients with Opportunistic Infections

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(Reference: vol 9, p. 59)

Medical Officer Comment:

Candida was more frequently seen in the younger age groups. The profile of adverse events reported is similar to that reported in adult renal transplant recipients.

2.5.2.7 Laboratory Abnormalities

In the first 30 days of the study, there were no abnormal laboratory results of clinically meaningful significance, or which were outside the range that is expected as a result of a prior history of renal failure. Seven patients had hemoglobin values below the medically acceptable level of 6.5 g/dL (four in the 6 – < 12 year and three in the 12 – 18 year groups); these were not unexpected, as all occurred within the first eight days posttransplant.

From study day 31 to 180, five patients had maximum AP (alkaline phosphatase) values above the medically acceptable level of ≥ 600 U/L. These were not considered clinically significant, since increased AP levels reflect a high rate of bone turnover, which is common in young children.

One patient (No. 53393) showed platelets levels below the acceptable minimum ($< 25 \times 10^3 / \mu\text{L}$). A very low platelet count of 56,000/ml was reported at baseline for this patient; after 40 days on MMF thrombocytopenia worsened and study drug was interrupted. The patient eventually withdrew from the study due to severe thrombocytopenia.

**Patients with Laboratory Values Above/Below Minimum/Maximum Levels
(Day 31-180)**

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(Reference: Vol 9, p. 62)

From study day 181 to 365, one patient (No. 53122, < 2 years of age) had a value below the acceptable minimum value for ANC ($< 0.5 \times 10^3 / \mu\text{L}$). This patient was HIV positive at baseline and experienced intercurrent illness while on study drug, with decreased WBC and ANC levels. MMF was discontinued due to neutropenia and leukopenia, and the patient was withdrawn from the study because of EBV infection.

One patient in the < 2 year subgroup had a hemoglobin value below the acceptable minimum value ($< 6.5 \text{ g/dL}$). On the same day the patient reported a severe AE for anemia, which was not considered related to MMF treatment.

**Patients with Laboratory Values Above/Below Minimum/Maximum Levels
(Day 181-365)**

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(Reference: Vol 9, p. 62)

Medical Officer Comment:

It appears that over time, patients' laboratory values return to normal. This was a pattern seen in the previous kidney transplant studies in adults.

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5 page(s) have been
removed because it
contains trade secret
and/or confidential
information that is not
disclosable.

4.0 Conclusions

The applicant has demonstrated the safety of CellCept at a dose of 600 mg/m² bid in combination with cyclosporine and prednisone for the prevention of acute rejection in pediatric renal transplant recipients. Efficacy data from a non-randomized, prospective study in 100 pediatric patients demonstrates similar efficacy rates of 6-month acute rejection and 12-month graft loss and death.

5.0 Labeling Recommendations

EFFICACY STATEMENTS IN PEDIATRIC RENAL TRANSPLANT RECIPIENTS:

THE FOLLOWING ARE LABELING REQUESTS FROM THE REVIEWING MEDICAL OFFICER (transmitted by FAX 12/XX/2000).

The text of the proposed label is presented followed by medical officer requests and comments.

I. CLINICAL STUDIES

Pediatrics: One open-label, safety and pharmacokinetic study of CellCept oral suspension 600 mg/m² bid (up to 1g bid) in combination with cyclosporine and corticosteroids was performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients (3 months to 18 years of age) for the prevention of renal allograft rejection. CellCept was well tolerated in pediatric patients (see ADVERSE REACTIONS), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1g bid CellCept capsules (see CLINICAL PHARMACOLOGY: Pharmacokinetics). The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 to <12 years, 12 to 18 years). The overall biopsy-proven rejection rate at 6 months and the [redacted] and patient death at 12 months posttransplant were similar to the rates observed in adult renal transplant patients.

1. Request: Please specify the rates of graft loss and death at 12 months in the last sentence above.

II. PRECAUTIONS:

Pediatric Use: Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, the recommended dose of CellCept oral suspension is 600 mg/m² bid (up to maximum of 1 g bid). Also see CLINICAL PHARMACOLOGY; CLINICAL STUDIES; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION. Safety and effectiveness in pediatric patients receiving allogeneic cardiac transplants have not been established.

2. Comment: This statement is acceptable to FDA.

III. ADVERSE EVENTS:

Pediatrics: The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with CellCept oral suspension 600 mg/m² bid (up to 1 g bid) were generally similar to those observed in adult patients dosed with

3. Requests:

a. In review of the data supplied by Roche, the rate of leukopenia (24%) appears to be the same as that seen in renal transplant patients in the US (23.2%).

b. It is recommended that Roche expand the information supplied regarding adverse events in pediatrics.

c. It is important information to give to the physician who is managing the renal transplant recipient.

d. While, it is generally the case that the types of adverse events are similar to those in adults, the frequencies are significantly higher, not just for the 4 events listed in the proposed labeling, but also for pain, abdominal pain, fever, infection, sepsis, hypertension, vomiting, respiratory tract infection, pharyngitis.

e. Finally, a comment should be made regarding the occurrence of malignancies in the pediatric studies.

f. The rate of gastrointestinal hemorrhage should be added to the PRECAUTIONS: General : section.

IV. DOSAGE AND administration: renal Transplantation.

PEDIATRICS: The recommended dose of CellCept oral suspension is 600mg/m² administered twice daily (up to a maximum daily dose of 2 g/10 mL oral suspension). Patients with a body surface area of 1.25 to 1.5 m² may be dosed with CellCept capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area >1.5

m 2 may be dosed with CellCept capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

4. Comment: this statement is acceptable to the medical reviewer.

These comments were transmitted to the sponsor.

Medical Officer Comment:

Creatinine clearance (ml/min/1.73m²) was calculated using the following formula, specifically developed for pediatric patients : $[(0.035 \times \text{Age [y]}) + 0.236] \times 100 / \text{serum creatinine [mg/dL]}$

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Appendix B Adverse Events Reported in $\geq 10\%$ of patients in Study MYCS2675.

(PAGE 1 OF 11)

SUMMARY OF PATIENTS WITH ADVERSE EVENTS
SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
ANY BODY SYSTEM	33 (100.0%)	34 (100.0%)	33 (100.0%)	100 (100.0%)
BODY SYSTEM				
BODY AS A WHOLE	33 (100.0%)	30 (88.2%)	33 (100.0%)	96 (96.0%)
DIGESTIVE SYSTEM	33 (100.0%)	28 (82.4%)	27 (81.8%)	88 (88.0%)
RESPIRATORY SYSTEM	29 (87.9%)	27 (79.4%)	23 (69.7%)	79 (79.0%)
UROGENITAL SYSTEM	28 (84.8%)	25 (73.5%)	24 (72.7%)	77 (77.0%)
METABOLIC AND NUTRITIONAL DISORDERS	28 (84.8%)	22 (64.7%)	26 (78.8%)	76 (76.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRDM UNVT -ABSUM_10PCT- (19OCT99,12:00) SAS V6.12 T-

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
BODY SYSTEM				
CARDIOVASCULAR SYSTEM	23 (69.7%)	21 (61.8%)	26 (78.8%)	70 (70.0%)
HEMIC AND LYMPHATIC SYSTEM	26 (78.8%)	23 (67.6%)	18 (54.5%)	67 (67.0%)
SKIN AND APPENDAGES	21 (63.6%)	23 (67.6%)	22 (66.7%)	66 (66.0%)
NERVOUS SYSTEM	16 (48.5%)	12 (35.3%)	17 (51.5%)	45 (45.0%)
SPECIAL SENSES	14 (42.4%)	11 (32.4%)	10 (30.3%)	35 (35.0%)
ENDOCRINE SYSTEM	7 (21.2%)	4 (11.8%)	12 (36.4%)	23 (23.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
ANY BODY SYSTEM	33 (100.0%)	34 (100.0%)	33 (100.0%)	100 (100.0%)
BODY SYSTEM PREFERRED TERM				
BODY AS A WHOLE	33 (100.0%)	30 (88.2%)	33 (100.0%)	96 (96.0%)
FEVER	26 (78.8%)	20 (58.8%)	22 (66.7%)	68 (68.0%)
PAIN	19 (57.6%)	14 (41.2%)	27 (81.8%)	60 (60.0%)
ABDOMINAL PAIN	13 (39.4%)	21 (61.8%)	14 (42.4%)	48 (48.0%)
SEPSIS	16 (48.5%)	11 (32.4%)	8 (24.2%)	35 (35.0%)
INFECTION	16 (48.5%)	9 (26.5%)	7 (21.2%)	32 (32.0%)
HEADACHE	2 (6.1%)	9 (26.5%)	11 (33.3%)	22 (22.0%)
FACE EDEMA	7 (21.2%)	2 (5.9%)	11 (33.3%)	20 (20.0%)
DRUG LEVEL INCREASED	5 (15.2%)	7 (20.6%)	7 (21.2%)	19 (19.0%)
ABDOMEN ENLARGED	8 (24.2%)	4 (11.8%)	5 (15.2%)	17 (17.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, [] REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
 SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

MMF SUSPENSION 600 mg/m² bid¹

	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS				
BODY SYSTEM PREFERRED TERM				
BODY AS A WHOLE (CONT.)				
BACK PAIN	0	1 (2.9%)	11 (33.3%)	12 (12.0%)
REACTION UNEVALUABLE	4 (12.1%)	3 (8.8%)	5 (15.2%)	12 (12.0%)
ASTHENIA	2 (6.1%)	3 (8.8%)	6 (18.2%)	11 (11.0%)
ASCITES	3 (9.1%)	0	6 (18.2%)	9 (9.0%)
ACCIDENTAL INJURY	1 (3.0%)	2 (5.9%)	4 (12.1%)	7 (7.0%)
CYST	0	0	4 (12.1%)	4 (4.0%)
DIGESTIVE SYSTEM	33 (100.0%)	28 (82.4%)	27 (81.8%)	88 (88.0%)
DIARRHEA	29 (87.9%)	23 (67.6%)	10 (30.3%)	62 (62.0%)
VOMITING	23 (69.7%)	15 (44.1%)	12 (36.4%)	50 (50.0%)
GUM HYPERPLASIA	8 (24.2%)	9 (26.5%)	13 (39.4%)	30 (30.0%)
NAUSEA	4 (12.1%)	11 (32.4%)	15 (45.5%)	30 (30.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRDM UNVT -ASUM_10PCT- (19OCT99,12:00) SAS V6.12 T-

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
BODY SYSTEM PREFERRED TERM				
DIGESTIVE SYSTEM (CONT.)				
CONSTIPATION	7 (21.2%)	5 (14.7%)	14 (42.4%)	26 (26.0%)
ANOREXIA	3 (9.1%)	9 (26.5%)	4 (12.1%)	16 (16.0%)
DYSPEPSIA	0	2 (5.9%)	10 (30.3%)	12 (12.0%)
GASTROENTERITIS	1 (3.0%)	4 (11.8%)	0	5 (5.0%)
RESPIRATORY SYSTEM	29 (87.9%)	27 (79.4%)	23 (69.7%)	79 (79.0%)
INFECTION	18 (54.5%)	16 (47.1%)	15 (45.5%)	49 (49.0%)
COUGH INCREASED	14 (42.4%)	13 (38.2%)	10 (30.3%)	37 (37.0%)
PHARYNGITIS	8 (24.2%)	10 (29.4%)	7 (21.2%)	25 (25.0%)
RHINITIS	11 (33.3%)	6 (17.6%)	5 (15.2%)	22 (22.0%)
LUNG EDEMA	5 (15.2%)	4 (11.8%)	3 (9.1%)	12 (12.0%)
RESPIRATORY DISORDER	4 (12.1%)	2 (5.9%)	2 (6.1%)	8 (8.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRDM UNVT -AESUM_10PCT- (19OCT99,12:00) SAS V6.12 T-

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
BODY SYSTEM PREFERRED TERM				
RESPIRATORY SYSTEM (CONT.)				
SINUSITIS	1 (3.0%)	4 (11.8%)	1 (3.0%)	6 (6.0%)
UROGENITAL SYSTEM	28 (84.8%)	25 (73.5%)	24 (72.7%)	77 (77.0%)
URINARY TRACT INFECTION	16 (48.5%)	15 (44.1%)	9 (27.3%)	40 (40.0%)
HEMATURIA	7 (21.2%)	8 (23.5%)	7 (21.2%)	22 (22.0%)
DYSURIA	3 (9.1%)	7 (20.6%)	6 (18.2%)	16 (16.0%)
OLIGURIA	6 (18.2%)	2 (5.9%)	6 (18.2%)	14 (14.0%)
PYELONEPHRITIS	4 (12.1%)	3 (8.8%)	3 (9.1%)	10 (10.0%)
KIDNEY TUBULAR NECROSIS	1 (3.0%)	2 (5.9%)	6 (18.2%)	9 (9.0%)
URINARY TRACT DISORDER	3 (9.1%)	1 (2.9%)	4 (12.1%)	8 (8.0%)
HYDRONEPHROSIS	4 (12.1%)	1 (2.9%)	1 (3.0%)	6 (6.0%)
HYDROURETER	4 (12.1%)	2 (5.9%)	0	6 (6.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRM LMVT -ABSM_10PCT- (19OCT99,12:00) SAS V6.12 T-

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
 SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq$ 10% FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
BODY SYSTEM PREFERRED TERM				
UROGENITAL SYSTEM (CONT.)				
KIDNEY FUNCTION ABNORMAL	0	1 (2.9%)	5 (15.2%)	6 (6.0%)
URINARY INCONTINENCE	1 (3.0%)	4 (11.8%)	0	5 (5.0%)
METABOLIC AND NUTRITIONAL DISORDERS	28 (84.8%)	22 (64.7%)	26 (78.8%)	76 (76.0%)
CREATININE INCREASED	11 (33.3%)	10 (29.4%)	10 (30.3%)	31 (31.0%)
HYPOPHOSPHATEMIA	7 (21.2%)	11 (32.4%)	11 (33.3%)	29 (29.0%)
HYPOKALEMIA	10 (30.3%)	5 (14.7%)	7 (21.2%)	22 (22.0%)
ACIDOSIS	11 (33.3%)	4 (11.8%)	6 (18.2%)	21 (21.0%)
EDEMA	10 (30.3%)	6 (17.6%)	5 (15.2%)	21 (21.0%)
HYPERVOLEMIA	5 (15.2%)	4 (11.8%)	11 (33.3%)	20 (20.0%)
PERIPHERAL EDEMA	4 (12.1%)	5 (14.7%)	11 (33.3%)	20 (20.0%)
HYPERKALEMIA	7 (21.2%)	3 (8.8%)	6 (18.2%)	16 (16.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRDM (MWT -ASUM_10PCT- (19OCT99,12:00) SAS V6.12 T-

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS				
BODY SYSTEM PREFERRED TERM				
METABOLIC AND NUTRITIONAL DISORDERS (CONT.)				
HYPOMAGNESEMIA	5 (15.2%)	5 (14.7%)	5 (15.2%)	15 (15.0%)
HYPOPROTEINEMIA	7 (21.2%)	3 (8.8%)	3 (9.1%)	13 (13.0%)
DEHYDRATION	6 (18.2%)	2 (5.9%)	4 (12.1%)	12 (12.0%)
HYPOXIA	4 (12.1%)	2 (5.9%)	2 (6.1%)	8 (8.0%)
HYPERLIPEMIA	2 (6.1%)	1 (2.9%)	4 (12.1%)	7 (7.0%)
HYPERCHOLESTEREMIA	1 (3.0%)	0	5 (15.2%)	6 (6.0%)
HYPONATREMIA	4 (12.1%)	1 (2.9%)	0	5 (5.0%)
CARDIOVASCULAR SYSTEM	23 (69.7%)	21 (61.8%)	26 (78.8%)	70 (70.0%)
HYPERTENSION	19 (57.6%)	19 (55.9%)	22 (66.7%)	60 (60.0%)
TACHYCARDIA	5 (15.2%)	2 (5.9%)	5 (15.2%)	12 (12.0%)
HYPOTENSION	3 (9.1%)	2 (5.9%)	6 (18.2%)	11 (11.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRDM UNWT -ASUM_10DCT- (19OCT99,12:00) SAS V6.12 T-

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² b.i.d. ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
BODY SYSTEM PREFERRED TERM				
CARDIOVASCULAR SYSTEM (CONT.)				
VASCULAR DISORDER	2 (6.1%)	1 (2.9%)	5 (15.2%)	8 (8.0%)
HEMIC AND LYMPHATIC SYSTEM	26 (78.8%)	23 (67.6%)	18 (54.5%)	67 (67.0%)
ANEMIA	17 (51.5%)	11 (32.4%)	9 (27.3%)	37 (37.0%)
LEUKOPENIA	10 (30.3%)	10 (29.4%)	4 (12.1%)	24 (24.0%)
THROMBOCYTOPENIA	4 (12.1%)	2 (5.9%)	2 (6.1%)	8 (8.0%)
SKIN AND APPENDAGES	21 (63.6%)	23 (67.6%)	22 (66.7%)	66 (66.0%)
HIRSUTISM	10 (30.3%)	11 (32.4%)	13 (39.4%)	34 (34.0%)
RASH	8 (24.2%)	6 (17.6%)	4 (12.1%)	18 (18.0%)
ACNE	1 (3.0%)	1 (2.9%)	11 (33.3%)	13 (13.0%)
HERPES SIMPLEX	2 (6.1%)	5 (14.7%)	4 (12.1%)	11 (11.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRDM UNVT -ARSDM_10PCT- (19OCT99,12:00) SAS V6.12 T-

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
 SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
BODY SYSTEM PREFERRED TERM				
SKIN AND APPENDAGES (CONT.)				
SKIN BENIGN NEOPLASM	1 (3.0%)	3 (8.8%)	4 (12.1%)	8 (8.0%)
HERPES ZOSTER	1 (3.0%)	2 (5.9%)	4 (12.1%)	7 (7.0%)
NERVOUS SYSTEM	16 (48.5%)	12 (35.3%)	17 (51.5%)	45 (45.0%)
TREMOR	1 (3.0%)	5 (14.7%)	13 (39.4%)	19 (19.0%)
AGITATION	8 (24.2%)	1 (2.9%)	2 (6.1%)	11 (11.0%)
ANXIETY	3 (9.1%)	1 (2.9%)	5 (15.2%)	9 (9.0%)
NERVOUSNESS	5 (15.2%)	1 (2.9%)	2 (6.1%)	8 (8.0%)
PARESTHESIA	0	2 (5.9%)	4 (12.1%)	6 (6.0%)
DEPRESSION	1 (3.0%)	0	4 (12.1%)	5 (5.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT. () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRDM UNVT -ASUM_109CT- (19OCT99,12:00) SAS V6.12 T-

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SUMMARY OF PATIENTS WITH ADVERSE EVENTS
SUBSET OF EVENTS WITH OCCURRENCE RATE $\geq 10\%$ FOR AT LEAST ONE OF THE TREATMENT GROUPS

ALL INVESTIGATORS

	MMF SUSPENSION 600 mg/m ² bid ¹			
	< 6 YRS	6-<12 YRS	12-18 YRS	TOTAL
TOTAL PATIENTS IN SUMMARY	33	34	33	100
	NO. (%) OF PATIENTS WITH ONE OR MORE ADVERSE EVENTS			
BODY SYSTEM				
PREFERRED TERM				
SPECIAL SENSES				
OTITIS MEDIA	14 (42.4%)	11 (32.4%)	10 (30.3%)	35 (35.0%)
EAR DISORDER	9 (27.3%)	8 (23.5%)	6 (18.2%)	23 (23.0%)
	6 (18.2%)	1 (2.9%)	3 (9.1%)	10 (10.0%)
ENDOCRINE SYSTEM				
CUSHINGS SYNDROME	7 (21.2%)	4 (11.8%)	12 (36.4%)	23 (23.0%)
	6 (18.2%)	3 (8.8%)	11 (33.3%)	20 (20.0%)

NOTE: COSTART THIRD EDITION PREFERRED TERMS AND BODY SYSTEMS.

¹MMF DOSE ADMINISTERED BASED ON BODY SURFACE AREA OF PATIENT, () REFERS TO AGE (IN YEARS) OF PATIENT AT ENROLLMENT.

SOURCE: IRM UNVT -ARJUM_10PCT- (19OCT99,12:00) SAS V6.12 T-