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APPLICATION NUMBER:

50-722/S-005

50-723/S-005

50-758/S-004

50-759/S-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 50-722/S-005 50-723/S-005 50-758/S-004 50-759/S-006	**Submission Date:** 10/1/99
Generic Name, Strength and Formulation:	Mycophenolate Mofetil 250 mg Capsules
Brand Name: Cellcept®	**Date Assigned:** 10/13/99
Applicant: Roche	**Final Review:** 7/18/2000
Submission Code: S	**Reviewer:** Kofi A. Kumi, Ph.D.

Synopsis

The applicant submitted an efficacy supplement to use Cellcept for prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants. Cellcept (mycophenolate mofetil, MMF) is already approved for prophylaxis of organ rejection in renal and cardiac allograft recipients when administered in combination with cyclosporine and corticosteroids. The applicant's rationale for extending the indication to include hepatic transplant patients is the postulation that while certain aspects of rejection may differ from organ to organ, the basic immunological mechanisms of rejection are activated in the presence of any allograft, and thus the pharmacologic effects of an immunosuppressant observed in one transplant setting is likely to apply in other settings. The absorption, distribution, metabolism and excretion of MMF in healthy and renal transplant patients were described in NDA 50,722 and cross-referenced in this review. MMF is hydrolyzed to mycophenolic acid (MPA), the active moiety. MPA is a potent and specific inhibitor of de novo purine synthesis which blocks the proliferation of both T and B lymphocytes. MPA undergoes conversion to an inactive glucuronide (MPAG) which is eventually excreted in urine. MPAG is also excreted in bile and undergoes enterohepatic recycling as MPA.

In this application, the applicant submitted a pivotal efficacy study in which pharmacokinetics (PK) of MMF in a subgroup of hepatic transplant patients were evaluated. A multiple dose pharmacokinetic interaction study between MMF and tacrolimus was also submitted in this application. The applicant referenced two studies submitted to NDA 50,722 (ICM 1812) and 50,758 (IID2104). For this application, the dose for hepatic transplant recipients was selected to achieve MPA AUC(0-12h) similar to that observed in renal transplant recipients receiving 1 gm bid (25 – 40 μg*h/mL). The dosage formulations used in the pivotal clinical studies are the approved 250 mg capsule formulation and the 500 mg/mL lyophilized powder for intravenous infusion.

The primary questions the reviewer focused on during this review were 1) What is the pharmacokinetics of MPA and MPAG in hepatic transplant patients 2) How does the pharmacokinetics in hepatic transplant patients compare to renal and cardiac transplant patients 3) Is there evidence of a relationship between AUC and/or Cmax and biopsy proven rejection.

The pharmacokinetic parameters for MPA in patients who were administered intravenous MMF 1gm twice a day (BID) followed by oral MMF 1.5 gm BID in the pivotal study is provided in the following table

Pharmacokinetic Parameters of MPA after Administration of IV MMF 1gm BID (over 2 hours) and 1.5 gm Oral MMF

Parameter	IV MMF[a] (N=22)	1st Oral Dose (N=20)	6-month Oral Dose (N= 6)
	Mean ± SD		
AUC(0-12h) (μg*h/mL)[b]	34.0 ± 17.4	29.2 ± 11.9	49.3 ± 14.8
Cmax (μg/mL)[b]	17.0 ± 12.7	13.1 ± 6.76	19.1 ± 11.7
Tmax (h)	1.50 ± 0.52	1.15 ± 0.43	1.54 ± 0.51

Mean MPA AUC and Cmax were higher after 6 months than that observed after the 1st oral dose. There was large variability in the pharmacokinetic parameters. There was a decrease in mean AUC when the patients were switched from IV to oral Cellcept in hepatic transplant patients. However, the decrease in exposure is not expected to be clinically significant. The dosing regimen used in the pivotal clinical trial (1gm IV BID followed by 1.5 gm po BID) achieved the targeted AUC of 25 - 40 μg/mL observed in renal transplant patients. However, it is not known if the exposure (AUC) obtained would correspond to successful clinical outcome in liver transplant patients (see medical officer's review for safety and efficacy results).

Mean AUC of MPA was similar after IV administration in hepatic and renal transplant patients. In stable transplant patients, mean AUC of hepatic transplant patients tended to be lower after 6 months than that observed for renal (after 3 months) but was similar to that for cardiac transplant (after 6 months) patients. In all transplant types, the mean AUC(0-12h) tended to increase from the immediate transplant period to the late transplant period. With chronic oral dosing (≥ 6 months) in hepatic patients, there was a 1.7- fold increase in mean MPA AUC(0-12h) compared to the early posttransplant period. Mean MPA AUC(0-12h) in renal and cardiac transplant recipients, after chronic oral dosing of MMF, also has been reported to increase also by 1.7-fold and 1.5-fold, respectively.

The studies in hepatic transplant patients were not designed to adequately evaluate the pharmacokinetic/pharmacodynamic (PK/PD) relationship of MPA concentration and rejection. However, an exploratory examination of the data did not reveal an evidence of a correlation between organ rejection and mean MPA AUC, Cmax and pre-dose concentration (troughs).

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What is the Pharmacokinetics of MPA and MPAG in hepatic transplant patients

The principal study the reviewer relied on to evaluate the PK of MPA and MPAG in hepatic transplant patients was the pivotal clinical study in which pharmacokinetic evaluation was conducted in a subset of patients. PK profiles (over a 12-hour period) for MPA and MPAG in hepatic transplant patients were determined on the last day of intravenous (IV) infusion, the first day of oral dosing and after chronic oral dosing (at approximately 6 months post transplantation). A supportive study that described the pharmacokinetics of MPA and MPAG after IV and oral (po) administration with different dosing regimens was also provided. A brief overview of these studies are described as follows:

Study Title (Protocol MYCS2646): A randomized, double-blind comparative study of the clinical efficacy and safety of intravenous and oral mycophenolate mofetil and azathioprine, each in combination with cyclosporine (Neoral®) and corticosteroids in liver transplant recipients: Pharmacokinetic report (Volume 7 page 1)

Objectives: The primary purpose of this study was to compare the safety and efficacy of a treatment regimen of MMF (intravenous followed by oral) in conjunction with cyclosporine (Neoral®) and corticosteroids, to that of standard treatment consisting of azathioprine, cyclosporine and corticosteroids in liver allograft recipients.

Study Design: All patients were asked to participate in a 2-hour blood sampling for MPA and MPAG pharmacokinetic assessments (mini PK profiles). Approximately 30 patients were asked to participate in three 12-hour blood samplings (full PK profiles) for MPA and MPAG PK assessments; the three samplings occurred on the last day of intravenous dosing, the first day of oral dosing and after chronic oral dosing (at approximately 6 months post-transplant). To prevent unblinding, blood samples were not analyzed at study centers; all samples were sent to a central independent laboratory for analysis. The first dose (1gm) of intravenous (IV) MMF/Placebo infusion was started within 24 hours following transplant surgery. Each subsequent MMF/Placebo was given 12 hours after the start time of the previous infusion. Infusions were administered over 2-hours. Infusions continued until at least 8 doses were administered. Patients could receive their first oral dose of MMF/Placebo on day 5 post-transplantation. The dose of oral MMF/placebo was 1.5 gm (6 capsules) every 12 hours. Patients stayed on this dose for the remainder of the study.

The first dose of azathioprine /placebo was started within 24 hours following transplant surgery. The initial dose of azathioprine/placebo was within the range of 1-2 mg/kg/day. Each subsequent azathioprine infusion was given 24 hours after the start time of the previous infusion. Infusions continued until oral study capsules were tolerated. The daily oral dose of azathioprine was within 1-2 mg/kg/day.

Patients were treated with cyclosporine (Neoral®) according to the standard of care at the respective center. Cyclosporine trough blood concentrations of 200 – 400 ng/mL were maintained from the time of transplantation through week 8, unless other levels were medically warranted. Thereafter, trough cyclosporine target blood concentrations of 100 – 300 ng/mL were maintained.

All patients received a full course of high-dose IV steroids at the time of transplantation, followed by an oral steroid taper according to the standard practice at the respective center.

Patients who were converted to tacrolimus therapy, remained in the study continuing study drug assignment. Whole blood tacrolimus trough levels were maintained in the range of 5 to 15 ng/mL. Antacids were not permitted within 2 hours of oral MMF or azathioprine dosing.

Full pharmacokinetic blood sampling began at the time of the final morning intravenous dose of MMF or its placebo. The second PK blood sampling occurred 24 hours later, beginning at the time of the first morning oral dose of MMF or its placebo. The 3rd 12-hours later, beginning at the time of the first morning oral dose of MMF or its placebo. The 4th 12-hour PK assessment occurred at study month 6 (± 1 month). For these PK profiles, blood samples were taken immediately pre-dose (0 mins), at 30, 45, 60, 75, 90, 120 and 180 minutes and at 4, 6, 8 and 12 hours after the start of intravenous dosing or administration of the oral dose.

After a patient had been on oral MMF (or its placebo) for at least three days, blood samples (5 mL each) were obtained immediately prior to morning oral dosing and at 20, 40, 75 and 120 minutes after dosing. Patients fasted from 10 pm until after collection of the 2-hour blood sample.

Analytical Methods:

Data Analysis: Noncompartmental methods were used to compute pharmacokinetic parameters. The primary comparison was between the AUC (0-12h) on the last day of morning IV dosing and the AUC (0-12h) on the first day of morning oral dosing on a natural log scale. In addition, the 6 month AUC (0-12h) was compared with the AUC (0-12h) values for the first oral dose.

Results: Twenty-two patients who received MMF participated in the 12-hour pharmacokinetic (PK) assessments; 22 patients profiles were collected for the last morning of intravenous (IV) MMF; 21 patient profiles were collected for the first oral dose of MMF; and 14 patient profiles were collected at month 6 post-transplant. The subset of patients who participated in the PK studies consisted of 20 Caucasians (15 males; 5 females) and 2 Hispanics. The mean age and weight of the patients were 49.3 years (range 29 – 68 years, with 2 ≥ 65 years) and 80.5 kg (range of 41 – 130 kg), respectively. On the first day of PK sampling, all 22 patients received the nominal 1 gm IV dose; for PK sampling at the first oral dose, 20 patients received 1.5 gm MMF and one patient received 1.0 gm; at the 6-month PK sampling, 6 patients received 1.5 gm MMF and 8 patients received doses that ranged from 0.25 – 1.0 gm. The following table contains a summary of pharmacokinetic parameters for MPA

Parameter	IV MMF[a] (N=22)	1st Oral Dose (N=21)	6-month Oral Dose (N=14)
	Mean ± SD		
AUC(0-12h) (μg*h/mL)[b]	34.0 ± 17.4	31.0 ± 14.3	60.6 ± 18.4
Cmax (μg/mL)[b]	17.0 ± 12.7	13.2 ± 6.64	29.3 ± 17.2
Cmin (μg/mL)	0.85 ± 1.47	0.78 ± 0.71	2.45 ± 2.51
Tmax (h)	1.50 ± 0.52	1.13 ± 0.43	1.07 ± 0.60

[a] IV dose = 1g infused over 2 hours; [b] Data for oral dosing period normalized to 1.5g

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Log Transformed Ratios of MPA AUC(0-12h) and Cmax Comparing Intravenous to First Oral Dosing

Parameter	IV to Oral Ratio (%)	90% Confidence Interval	95% Confidence Interval
AUC (0-12h) (μg*h/mL)	111.6	92.5% - 134.6%	89.1% - 139.7%
Cmax (μg/mL)	129.1	94.4% - 176.7%	88.6% - 188.2%

There was about 12% and 29% increase in mean AUC and Cmax, respectively, when the IV was compared to the first oral dose regimen. These differences were not statistically significant; however, there was large variability in the data.

The following table contains the log transformed ratios for MPA AUC(0-12h) and Cmax comparing 6-month oral dosing to first oral dosing.

Log Transformed Ratios of MPA AUC(0-12h) and Cmax Comparing 6-month to First Oral Dosing

Parameter	Ratio of 6-month to first Oral (%)	90% Confidence Interval	95% Confidence Interval
AUC (0-12h) (μg*h/mL)	212.7	170.2% - 265.9%	162.7% - 278.2%
Cmax (μg/mL)	223.3	153.7% - 324.5%	142.6% - 349.9%

There was about 113% and 123% increase in mean AUC and Cmax, respectively when 6-month was compared to first oral dose regimen. The differences were statistically significant and there was large variability in the data.

A summary of the pharmacokinetic parameters for MPAG (MPA Equivalent Units) are contained in the following table

Summary of Mean MPAG (MPA Equivalent Units) Computed Parameters

Parameter	IV MMF[a] (N=22)	1st Oral Dose (N=21)	6-month Oral Dose (N=14)
	Mean ± SD		
AUC(0-12h) (μg*h/mL)[b]	616 ± 407	809 ± 485	940 ± 379
Cmax (μg/mL)[b]	70.7 ± 36.0	90.9 ± 45.1	109 ± 37.2
Cmin (μg/mL)	37.6 ± 32.1	48.3 ± 37.1	58.4 ± 31.4
Tmax (h)	2.38 ± 0.584	2.36 ± 0.991	2.74 ± 1.37

Log Transformed Ratios of MPAG (MPA Equivalent Units) AUC(0-12h) and Cmax Comparing IV to First Oral Dosing

Parameter	Ratio of IV to first Oral (%)	90% Confidence Interval	95% Confidence Interval
AUC (0-12h) (μg*h/mL)	73.0	64.4% - 82.8%	62.8% - 84.9%
Cmax (μg/mL)	77.8	68.6% - 88.1%	66.9% - 90.4%

The mean MPAG (MPA equivalent units) AUC (0-12h) and Cmax for patients receiving 1 g IV MMF were about 27% and 22%, respectively, lower than those for patients receiving their first 1.5g oral dose. Although, these differences were statistically significant, the clinical significance is unknown. There were relatively modest increases in the PK parameters for MPAG compared to that seen for MPA. These modest increase in MPAG could suggest a reduction in the glucoronidation capacity of MPA to MPAG of the transplanted livers.

The following table contains the log transformed data for mean MPAG (MPA equivalents units) AUC(0-12h) and Cmax comparing 6-month to first oral dosing

Log Transformed Ratios of MPAG (MPA Equivalent Units) AUC (0-12h) and Cmax Comparing 6-month to First Oral Dosing

Parameter	Ratio of 6-month to first Oral (%)	90% Confidence Interval	95% Confidence Interval
AUC (0-12h) (μg*h/mL)	128.0	110.2% - 148.7%	106.9% - 153.2%
Cmax (μg/mL)	127.4	109.7% - 147.8%	106.5% - 152.3%

The mean MPAG (MPA equivalent units) AUC (0-12h) and Cmax for the month 6 oral dose increased by about 28% and 27%, respectively when compared to the AUC and Cmax after the first oral dose.

The following table provides a summary of AUC, Cmax and Cmin according to gender.

Parameter	Last Day IV MMF		First Day of Oral MMF		Month 6 of Oral MMF	
	Male	Female	Male	Female	Male	Female
	Mean ± SD		Mean ± SD		Mean ± SD	
AUC (0-12h) (μg*h/mL)	36.2 ± 19.6	28.1 ± 7.59	32.0 ± 14.9	28.5 ± 13.7	62.8 ± 20.5	55.2 ± 12.6
Cmax (μg/mL)	18.7 ± 14.5	12.4 ± 2.74	13.8 ± 11.7	11.7 ± 6.44	32.2±19.3	22.1 ± 8.51
Cmin (μg/mL)	0.93 ± 1.68	0.64 ± 0.71	0.75 ± 0.76	0.85 ± 0.65	1.61 ± 0.84	4.56 ± 4.10

Females tended to have lower mean AUC and Cmax but these differences were not statistically significant. Cmin following oral dosing tended to be higher in females than males; however, there was large inter-patient variability in the data, especially Cmin.

In patients who did not participate in the 12-hour pharmacokinetic profile assessment, a 2-hour profile was obtained. The applicant estimated the 12-hour MPA AUC from the two hour profiles. The MPA AUC (0-12h) was estimated from 0-2 hour profiles by estimating the 6, 8 and 12 hour concentration to be uniformly equal to 0.14 (μg/mL) + 1.25Co, where Co is the pre-dose MPA concentration, applying the linear trapezoidal rule. The following is day 14 pharmacokinetic parameters estimated using the 2- hour profile.

Mini (0-2h) Profile: Mean MPA Computed Parameter Summary

Parameters	[a]Day 14th Oral MMF	
	N	Mean ± SD
AUC(0-2h)(μg*h/mL)	110	9.24 ± 5.87
Estimated[b] AUC(0-12h) (μg*h/mL)	110	26.0 ± 11.3
Cmax (μg/mL)	118	7.79 ± 5.58
Tmax (0-2h) (h)	118	1.16 ± 0.618

[a] Mini-profiles taken, on average, at day 14 posttransplant
[b] Estimated from the mini (0-2h) profile

The plot of MPA AUC(0-12h) estimated by the mini-profile versus that estimated by data from the 0-12 hour profile is provided in the figure on the following page. The points are distributed about the line of identity which may suggest no bias in the estimation. The mean and standard deviation of the ratio of MPA AUC(0-12h estimated from 0-2h profiles)/MPA AUC(0-12h estimated from 0-12h) were 1.07 ± 0.19 with a 95% CI (0.974, 1.16). The applicant concludes that the 0-2 hr mini-profiles perform reasonable well to estimate the full 12 hour profile for MPA. The reviewer accepts the applicant's conclusion.

A summary of standardized cyclosporine trough concentrations is in the following tables. The mean standardized trough concentrations appeared similar in both arms of the study.

Conclusions: The mean AUC(0-12h) after administration of the 1 gm IV dose appeared to be similar to that obtained after the first oral 1.5 gm dose. However, Cmax was higher for the IV dose compared to the first oral dose. The mean MPAG(0-12h) and Cmax were significantly lower for the IV dose compared to the first oral dose. Cmin was not significantly different but there was large inter-patient variability in the data. Comparing the AUC(0-12h) at 6 months posttransplant versus the first oral dose, there was 1.6 to 2-fold increase in MPA AUC(012h); there was also a modest increase in MPAG AUC(0-12h) over the oral dosing period. There was no statistically significant correlation between age or body weight and MPA AUC or Cmax. In this study, the mean AUC(0-12h) for females was numerically lower than for males. For hepatic transplant patients, in the immediate post transplant period (< 14 days) an intravenous dose of MMF 1 gm and an oral dose of 1.5gm bid achieved a targeted AUC of 25- 40 μg/mL.

Reviewer's Comments:

1) As observed in other transplant indications for Cellcept, MPA AUC and Cmax were significantly higher after 6 months than that observed at the 1st oral dose.
2) There was large variability in the pharmacokinetic parameters
3) There was small decrease in AUC when the patients were switched from IV to oral Cellcept in hepatic patients. The decrease in AUC is not expected to be clinically significance. The AUCs were within the observed concentrations for MPA in renal transplant patients after Cellcept administration.
4) AUC (0-2h) reasonably estimated AUC (0-12h).
5) The dosing regimen used in the pivotal clinical trial (1gm IV BID followed by 1.5 gm po BID) achieved the targeted AUC speculated by the applicant. However, it is not known if the exposure (AUC) obtained would correspond to successful clinical outcome in liver (see medical officer's review for safety and efficacy results).

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Summary of Standardized Cyclosporine Trough Concentration By Visit

MYCS264611

SUMMARY OF STANDARDIZED CYCLOSPORINE TROUGH CONCENTRATION BY VISIT

ALL INVESTIGATORS

STUDY VISIT	AZA 1-2 mg/kg/day	MMF 1.5 gm BID
DAY 7		
PATIENTS IN STUDY	281	268
PATIENTS WITH MISSING DATA	20	14
BELOW RANGE	[redacted]	
LOW - MID RANGE		
MID - HIGH RANGE		
ABOVE RANGE		
MEAN	1.24	1.26
SD	0.78	0.74
MEDIAN	1.07	1.12
RANGE	[redacted]	
DAY 14		
PATIENTS IN STUDY	269	250
PATIENTS WITH MISSING DATA	26	17
BELOW RANGE	[redacted]	
LOW - MID RANGE		
MID - HIGH RANGE		
ABOVE RANGE		
MEAN	1.45	1.52
SD	0.73	0.86
MEDIAN	1.36	1.40
RANGE	[redacted]	

NOTE: STANDARDIZED CYCLOSPORINE LEVEL = RATIO OF CYCLOSPORINE TROUGH CONCENTRATION TO THE MIDPOINT OF THE TARGET RANGE OF THE ASSAY.

MYCS264611 [redacted]

SUMMARY OF STANDARDIZED CYCLOSPORINE TROUGH CONCENTRATION BY VISIT

ALL INVESTIGATORS

STUDY VISIT	AZA 1-2 mg/kg/day	MMF 1.5 gm BID
DAY 28		
PATIENTS IN STUDY	247	237
PATIENTS WITH MISSING DATA	24	20
BELOW RANGE	[redacted]	[redacted]
LOW - MID RANGE		
MID - HIGH RANGE		
ABOVE RANGE		
MEAN	1.34	1.39
SD	0.67	0.73
MEDIAN	1.24	1.23
RANGE	[redacted]	
MONTH 2		
PATIENTS IN STUDY	224	217
PATIENTS WITH MISSING DATA	18	30
BELOW RANGE	[redacted]	
LOW - MID RANGE		
MID - HIGH RANGE		
ABOVE RANGE		
MEAN	1.24	1.21
SD	0.72	0.69
MEDIAN	1.12	1.11
RANGE	[redacted]	

NOTE: STANDARDIZED CYCLOSPORINE LEVEL = RATIO OF CYCLOSPORINE TROUGH CONCENTRATION TO THE MIDPOINT OF THE TARGET RANGE OF THE ASSAY.

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MYCS264611 [redacted]

SUMMARY OF STANDARDIZED CYCLOSPORINE TROUGH CONCENTRATION BY VISIT

ALL INVESTIGATORS

STUDY VISIT	AZA 1-2 mg/kg/day	MMF 1.5 gm BID
MONTH 3		
PATIENTS IN STUDY	211	202
PATIENTS WITH MISSING DATA	17	25
BELOW RANGE LOW - MID RANGE MID - HIGH RANGE ABOVE RANGE	[redacted]	
MEAN	1.17	1.13
SD	0.83	0.60
MEDIAN	1.05	1.05
RANGE	[redacted]	
MONTH 6		
PATIENTS IN STUDY	190	179
PATIENTS WITH MISSING DATA	23	23
BELOW RANGE LOW - MID RANGE MID - HIGH RANGE ABOVE RANGE	[redacted]	
MEAN	1.04	1.10
SD	0.81	1.11
MEDIAN	0.86	0.91
RANGE	[redacted]	

NOTE: STANDARDIZED CYCLOSPORINE LEVEL = RATIO OF CYCLOSPORINE TROUGH CONCENTRATION TO THE MIDPOINT OF THE TARGET RANGE OF THE ASSAY.

MYCS264611

SUMMARY OF STANDARDIZED CYCLOSPORINE TROUGH CONCENTRATION BY VISIT

ALL INVESTIGATORS

STUDY VISIT	AZA 1-2 mg/kg/day	MMF 1.5 gm BID
MONTH 9		
PATIENTS IN STUDY	171	163
PATIENTS WITH MISSING DATA	27	26
BELOW RANGE	[redacted]	
LOW - MID RANGE		
MID - HIGH RANGE		
ABOVE RANGE		
MEAN	0.92	0.89
SD	0.68	0.46
MEDIAN	0.79	0.83
RANGE	[redacted]	
MONTH 12		
PATIENTS IN STUDY	156	157
PATIENTS WITH MISSING DATA	16	28
BELOW RANGE	[redacted]	
LOW - MID RANGE		
MID - HIGH RANGE		
ABOVE RANGE		
MEAN	0.86	0.83
SD	0.59	0.47
MEDIAN	0.74	0.78
RANGE	[redacted]	

NOTE: STANDARDIZED CYCLOSPORINE LEVEL = RATIO OF CYCLOSPORINE TROUGH CONCENTRATION TO THE MIDPOINT OF THE TARGET RANGE OF THE ASSAY.

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6) Th pivotal clinical study provided sufficient information to evaluate the pharmacokinetics of MPA and MPAG after administration of MMF in hepatic transplant patients.

The applicant submitted a pilot study in which the pharmacokinetics of MPA and MPAG was evaluated after administration of different infusion regimens of IV MMF. The following is a summary of the study

Study Title (MYCS 2378, RRP-180256): Investigation of the pharmacokinetics and safety of mycophenolate mofetil given by intravenous infusion followed by oral dosing to liver allograft recipients (volume 4 page 55)

Objective: Primary: To determine the pharmacokinetics (PK) of mycophenolate mofetil (MMF), mycophenolic acid (MPA) and mycophenolic acid glucuronide (MPAG) and safety for three different infusion schedules of intravenous MMF, followed by oral dosing at 4 g/day in liver patients.

Study Design: Forty five patients with a mean ± SD age and weight of 50.9 ± 10.7 (range: 18 – 67) years and 79.9 ± 19.9 (range: 46.0 – 123.6) kg participated in this multicenter, randomized, open-label, parallel group study. Liver allograft recipients received intravenous MMF (4g/day, within 24 hour of transplantation) for approximately 7 days, followed by oral MMF (4 g/day) for up to 3 years. Patients were randomized to one of the following infusion regimens: 1) 2 g MMF bid, administered as two 80-min infusions; (II) 2 g MMF bid; administered as two 3-h infusions; (III) 1 g MMF qid, administered as a continuous infusion. Plasma samples were taken to determine the pharmacokinetics of MMF, MPA and MPAG during the three different infusion schedules of IV MMF and during the oral dosing period. The day 7 and 8 PK profiles represented the last day of intravenous (IV) MMF dosing and the first day of oral MMF dosing, respectively. For full PK profiles collected between months 9 – 12, patients must have received exactly 2 g bid oral MMF for five consecutive days prior to blood sampling. For PK profiles collected after month 12, patients must have received exactly 1.5 g bid oral MMF for five consecutive days prior to blood sampling. PK profiles obtained after month 12 were only collected from patients at one study site. Urine samples were collected at specified times for the determination of MPA and MPAG concentrations.

Analytical Methods:

Results: Twenty three patients completed the study. The following table contains MPA AUC(0-12h), Cmax and Cmin for the three dosing regimens over the first eight days posttransplant

Summary of Plasma MPA AUC(0-12h), Cmax and Cmin at Study Days 1,7 and 8

	MMF Dosage Form	2 gm MMF bid 80 min infusion	2 gm MMF bid 3 hour infusion	1 gm MMF qid 6 hour infusion
	Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (n)
AUC(0-12h) (μg*h/mL)				
Day 1	IV	59.2 ± 19.5(12)	55.3 ± 22.0(17)	NC[a]
Day 7[b]	IV	39.6 ± 9.99(12)	43.3 ± 20.1(15)	41.4 ± 18.7[c]
Day 8[d]	Oral	30.9 ± 13.1(11)	29.8 ± 12.9(15)	27.1 ± 10.4
Cmax (μg/mL)				
Day 1	IV	34.8 ± 11.1(12)	18.5 ± 5.86(17)	5.43 ± 1.73(15)
Day 7	IV	22.9 ± 7.31(12)	14.2 ± 11.9(15)	4.22 ± 2.41(13)
Day 8	Oral	9.92 ± 8.35(12)	8.54 ± 5.75(15)	7.14 ± 3.40(14)
Cmin (μg/mL)				
Day 1	IV	NC	NC	NC
Day 7	IV	0.60 ± 0.34(12)	0.68 ± 0.45(15)	3.71 ± 2.25(13)
Day 8	Oral	0.78 ± 0.51(12)	0.98 ± 1.02(15)	2.07 ± 1.02(14)

NC[a] = not calculated due to limited sampling
[b]or last day of intravenous (IV) dosing
[c]computed by multiplying AUC(0-6h) by 2
[d]or first dose of oral dosing

MPA AUC(0-12h) and Cmax are higher on day 1 than day 7 after IV infusion of MMF. The applicant attributes this observation to changing hepatic function of the newly transplanted liver in the immediate post transplant period.

When comparing day 7 to day 8 values, mean MPA AUC(0-12h) for the infusion regimens declined during the transition from IV to oral dosing. MPA AUC(0-12h) after IV administration over 80 mins, 3 hour and 6 hour infusions were higher by 32.7%, 45.3% and 60.1%, respectively when compared to the values obtained on day 8 after oral administration. During the transition from IV to oral (day7/day8), the mean Cmax values decline for the 80 and 3 hour infusion group but increased for the 6-hour (continuous) infusion group. The increase in mean Cmax for the 6-hour on day 8 compared to day 7 is expected because of the change in dosing schedule form 1 gm qid continuous infusion to 2 gm bid oral. For the 80 min and 3 hour infusion, Cmax was 130.7% and 59.4%, respectively higher after day 7 compared to day 8 administration. For the 6 hour continuous infusion, the day 7 Cmax was about 33% lower than day 8. Mean Cmin after the 80-min and 3hour IV infusion regimens were lower by 23% and 35%, respectively when compared

to the day 8 values. Mean Cmin after the 6-hour IV infusion was about 79% higher on day 7 compared to day 8 values.

A comparison of AUC(0-12h) and Cmax over time shows an overall increase in AUC(0-12h) and Cmax from day 14 through months 9,12,18 after oral administration. Mean MPA AUC(0-12h) after oral administration on day 90 and months 9,12,18 was about 117%, 183%, respectively higher when compared to the values computed for day 8. Mean MPA Cmax after oral administration on day 90 and months 9,12,18 was 166.8% and 202% higher than day 8 values.

The following table provides a summary of mean values after administration of oral Cellcept on days 8, 90, and months 9,12,18.

Mean Plasma MPA Computed Parameter Summary for Day 8 through months 9,12,18 for patients adjusted to 2 gm bid oral MMF

Parameter	Day 8	Day 14	Day 90	Months 9,12,18
	Mean ± SD			
AUC(0-12h) (μg*h/mL)	29.2 ± 11.9 (n = 40)	28.7 ± 11.5 (n = 37)	62.3 ± 24.6 (n = 31)	82.5 ± 33.6 (n= 10)
Cmax (μg/mL)	8.47 ± 5.98 (n = 41)	9.64 ± 6.31 (n = 38)	22.6 ± 12.4 (n = 31)	25.6 ± 8.48 (n = 11)
Cmin (μg/mL)	1.30 ± 1.19 (n = 41)	0.927 ± 0.553 (n = 38)	2.36 ± 1.90 (n = 32)	3.01 ± 2.19 (n = 12)
Clearance (L/min)	1.03 ± 0.525 (n = 40)	1.01 ± 0.425 (n = 37)	0.403 ± 0.193 (n = 32)	0.309 ± 0.109 (n = 10)

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The following table provides a summary of the pharmacokinetic parameters for MPAG after administration of IV MMF regimens.

	MMF Dosage Form	2 gm MMF bid 80 min infusion	2 gm MMF bid 3 hour infusion	1 gm MMF qid 6 hour infusion
	Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (n)
AUC(0-12h) (μg*h/mL)				
Day 1	IV	550 ± 121(12)	412 ± 118(17)	NC[a]
Day 7[b]	IV	1509 ± 754(12)	1016 ±922(15)	727 ± 330[d] (12)
Day 8[d]	Oral	1519 ±763(11)	912 ± 877(15)	895 ± 517(14)
Cmax (μg/mL)				
Day 1	IV	82.4 ± 48.1(12)	55.1 ±11.2(16)	25.6 ± 6.48(15)
Day 7	IV	169 ± 63.7(12)	118 ± 80.8(15)	61.5 ± 19.6(13)
Day 8	Oral	152 ± 67.4(12)	97.2 ± 76.8(15)	96.8 ± 39.3(14)
Cmin (μg/mL)				
Day 1	IV	NC	NC	NC
Day 7	IV	102± 62(12)	66.1 ± 74.1(15)	58.2 ± 17.6(13)
Day 8	Oral	110 ± 72.9(12)	63.0 ± 69.7(15)	96.8 ± 39.3(14)
%Drug excreted in urine as MPAG[e]				
Day 1	IV	45.3 ± 16.4(10)	46.7 ± 17.7(12)	34.4 ± 10.7(8)
Day 7	IV	80.9 ± 32(1)	80.2 ± 30.8(10)	124 ± 75.1(3)
Day 8	Oral	85.5 ± 62.1(7)	73.0 ± 24.4(10)	87.9 ± 36.1(9)

NC[a] = not calculated due to limited sampling; [b] or last day of intravenous (IV) dosing

[c] or first day of oral dosing; [d] computed by multiplying AUC(0-6h) by 2; [e] over 12 hours

The data indicate that mean MPAG AUC(0-12h) and Cmax are lower on day 1 than day 7. During the transition from IV to oral dosing, MPAG AUC(0-12h) for the 80 min, 3hr and 6 hr (continuous infusion) showed 2.2%, 10.0% increase and 24.2% decrease, respectively when day 7 is compared to day 8 values. The mean Cmax value during the IV/oral dosing transition, day 7 values for 80min, 3 hr infusion regimen were 10.8% and 21.4%, respectively and lower by about 34% for the 6hr- continuous infusion when day 7 were compared to day 8 values. The increase in Cmax after oral administration is attributed to change in dosing regimen from 1 gm qid to 2 gm bid. MPAG was the most abundant species recovered in the urine.

The following table provides the mean pharmacokinetic parameters of MPAG after oral administration of MMF.

Mean Plasma MPAG Computed Parameter Summary for Day 8 through months 9,12,18 for patients adjusted to 2 gm bid oral MMF

Parameter	Day 8	Day 14	Day 90	Months 9,12,18
	Mean ± SD			
AUC(0-12h) (μg*h/mL)	1073 ± 769 (n = 40)	1214± 714 (n = 37)	1299 ± 496 (n = 31)	1530 ± 374 (n= 10)
Cmax (μg/mL)	113 ± 66.8 (n = 41)	134 ± 63.7 (n = 38)	149 ± 45.7 (n = 31)	172 ± 35.0 (n = 11)
Cmin (μg/mL)	75.2 ± 64.0 (n = 41)	84.2 ± 59.7 (n = 38)	87.4 ± 41.4 (n = 32)	94.6 ± 31.7 (n = 12)
Clearance (L/min)	0.0347 ± 0.0209 (n = 40)	0.0268 ± 0.0135 (n = 37)	0.0193 ± 0.0093 (n = 31)	0.0157 ± 0.0041 (n = 10)

A comparison of the AUC(0-12) and Cmax show an overall increase in the parameters from day 14 through months 9,12,18. Mean MPAG AUC(0-12h) after oral administration on day 8 was about 13.1 %, 7 0% and 42.6% lower than the value obtained after day 14, day 90 and months 9,12,18, respectively after oral administration. It must be noted that the number of patients with pharmacokinetic data on months 9,12,18 are relatively small compared to those at day 8, 14 and 90. The applicant stated that because in the early posttransplant period, the patients are metabolically unstable, the pharmacokinetics of MMF show time dependency.

Mycophenolate Mofetil was unmeasurable in the plasma within 10 mins after cessation of infusion; the estimated half-life was less than 2 minutes.

Conclusion: Intravenous dosing of 4 gm per day using three different infusion regimens resulted in differences in plasma MPA Cmax. As expected, there was an inverse relationship between Cmax and the infusion duration. Mean MPA AUC(0-12h) values during the intravenous phase of the study were numerically different; however, the differences were not significant. At a fixed dose of 4 gm MMF/day, MPA AUC(0-12h) declined during the transition from IV to oral dosing in all three groups of infusion regimen that were studied.

The results of this study suggest that for liver transplant patients, plasma MPA and MPAG concentrations increase after transplantation. But unlike renal transplant patients, where the concentrations stabilized after 3 months, in liver transplant patients the MPA and MPAG concentrations continued to increase after 3 months.

MMF was rapidly converted to MPA in plasma after IV administration and was not detected shortly after the infusion was terminated. MPAG accounted for the majority of MMF recovered in the urine.

Reviewer's Comments: The trend in the pharmacokinetics of MPA and MPAG observed in this study is similar to that reported for renal and cardiac transplant patients. MPA and MPAG concentrations are time dependent and tended to increase after oral administration. However, in the liver transplant patients in this study it appears the concentrations do not stabilize after 3 months.

How does the pharmacokinetics in hepatic transplant compare to renal and cardiac transplant patients

The pharmacokinetic parameters obtained from the pivotal renal, cardiac and hepatic transplant patients are provided in the following tables.

Pharmacokinetic Parameters of MPA after Administration of Oral MMF 1.5gm BID

Parameter	Hepatic Transplant			Cardiac Transplant		
	MPA Mean ± SD (n)					
	Day 1 (20)	Last Day	≥ 6 months (6)	Day 1	Last Day	≥ 6 months
Tmax (hr)	1.15 ± 0.43	N/A	1.54 ± 0.51	2.02 ± 1.83 (17)	1.77 ± 1.32 (11)	1.12 ± 0.66 (52)
Cmax (µg/mL)	13.1 ± 6.76	N/A	19.1 ± 11.7	11.6 ± 7.45 (17)	11.51 ± 6.76 (11)	20.0 ± 9.35 (52)
AUC (µg*hr/mL	29.2 ± 11.9	N/A	49.3 ± 14.8	36.7 ± 11.9 (16)	43.3 ± 20.8 (9)	54.1 ± 20.4 (49)

Hepatic Transplant: Day 1- 1st day of oral dosing after IV dosing

Cardiac Transplant: Day 1- 1st day of oral dosing (without preceding IV dosing)

Last day: Day of discharge

Pharmacokinetic Parameters of MPAG after Administration of Oral MMF 1.5gm BID

Parameter	Hepatic Transplant			Cardiac Transplant		
	MPAG Mean ± SD (n)					
	1st Day (20)		≥ 6 months (6)	Day 1	Last Day	≥ 6 months
Tmax (hr)	2.44 ± 0.94	N/A	3.51 ± 1.53	5.78 ± 3.26 (17)	4.54 ± 4.25 (11)	2.52 ± 1.18 (54)
Cmax (μg/mL)	86.5 ± 41.4	N/A	93.4 ± 25.3	50.0 ± 15.7 (17)	94.1 ± 34.7 (11)	104 ± 34 (54)
AUC (μg*hr/mL	763 ± 448	N/A	775 ± 134	423 ± 137 (17)	963 ± 525 (9)	N/C

Hepatic Transplant: Day 1- 1st day of oral dosing after IV dosing

Cardiac Transplant: Day 1- 1st day of oral dosing (without preceding IV dosing)

Last day: Day of discharge

Pharmacokinetic Parameters of MPA after Administration of IV MMF 1 gm BID (over 2 hours) and 1.5 gm Oral MMF

Parameter	Hepatic Transplant			Renal Transplant		
	MPA Mean ± SD (n)					
	IV	Early (1st Oral Dose)	≥ 6months	IV	1st Oral Dose (Early <40 days)	≥ 3 months
Tmax (hr)	1.50 ± 0.52 (22)	1.15 ± 0.43 (20)	1.54 ± 0.51 (6)	1.58 ± 0.46 (31)	1.21± 0.81 (27)	0.90 ± 0.24 (23)
Cmax (μg/mL)	17.0 ± 12.7 (22)	13.1 ± 6.76 (20)	19.1 ± 11.7 (6)	12.0 ± 3.82 (31)	13.5 ± 8.18 (27)	24.1 ± 12.1 (23)
AUC (μg*hr/mL	34.0 ± 17.4 (22)	29.2 ± 11.9 (20)	49.3 ± 14.8 (6)	40.8 ± 11.4 (21)	38.4 ± 15.4 (27)	65.3 ± 35.4 (23)

Comparison of the IV dosing information indicated that mean AUC of MPA was similar after IV administration in hepatic and renal transplant patients. Comparison of the 1.5 gm oral MMF dose data shows that in the pivotal studies, the mean AUC(0-12h) during the early transplant period tended to be lower than that observed for the renal and cardiac patients. In stable transplant patients, mean AUC of hepatic transplant patients tended to be lower after 6 months than that observed for renal (after 3 months) but was similar to that for cardiac transplant (after 6 months)

patients. In all transplant types, the mean AUC(0-12h) tended to increase when the values for the immediate transplant period is compared with the late transplant period. With chronic oral dosing (≥ 6 months) in hepatic patients, there is a 1.7- fold increase in mean MPA AUC(0-12h) compared to the early posttransplant period. In other organ recipients treated with MMF a similar increase in mean MPA AUC(0-12h) (renal, 1.7 fold and cardiac, 1.5 fold) has been observed.

Is there evidence of a relationship between AUC and/or Cmax and biopsy proven rejection.

The studies in hepatic transplant patients were not designed to evaluate the pharmacokinetic/pharmacodynamic (PK/PD) relationship of MPA and rejection. Based on AUC(0-12h) estimated from mini-profiles (AUC(0-2h)) from 99 patients, an exploratory PK/PD relationship was attempted by examining the biopsy proven rejection and estimated AUC(0-12h). The table and figure on the following page provide MPA AUC, Cmax and pre-dose concentration for both the rejectors and non-rejectors. Examination of the mean values indicated that there was no evidence of a PK/PD relationship between the rejection and MPA AUC.

In stable renal transplant patients, MPA AUC was proposed to be a good predictor of rejection, with lower AUC values corresponding to higher rate of rejection. Such a correlation was not established in cardiac and hepatic transplant patients.

Mycophenolate-Tacrolimus Interaction

The applicant submitted in this application a multiple dose study drug interaction between tacrolimus and mycophenolate mofetil. The following is a brief summary of the study.

Study Title (MYCS063): The Effect of Multiple Doses (3 g per day) of Mycophenolate Mofetil on the Pharmacokinetics of [redacted] in Stable Hepatic Transplant Recipients (volume 14 page 1)

Objective: To evaluate the effect of the multiple doses of mycophenolate mofetil (MMF, 1.5 g BID) on steady state [redacted] pharmacokinetics in hepatic transplant patients in a stable clinical condition and the observation of tolerability data on the study population receiving [redacted] and MMF in combination

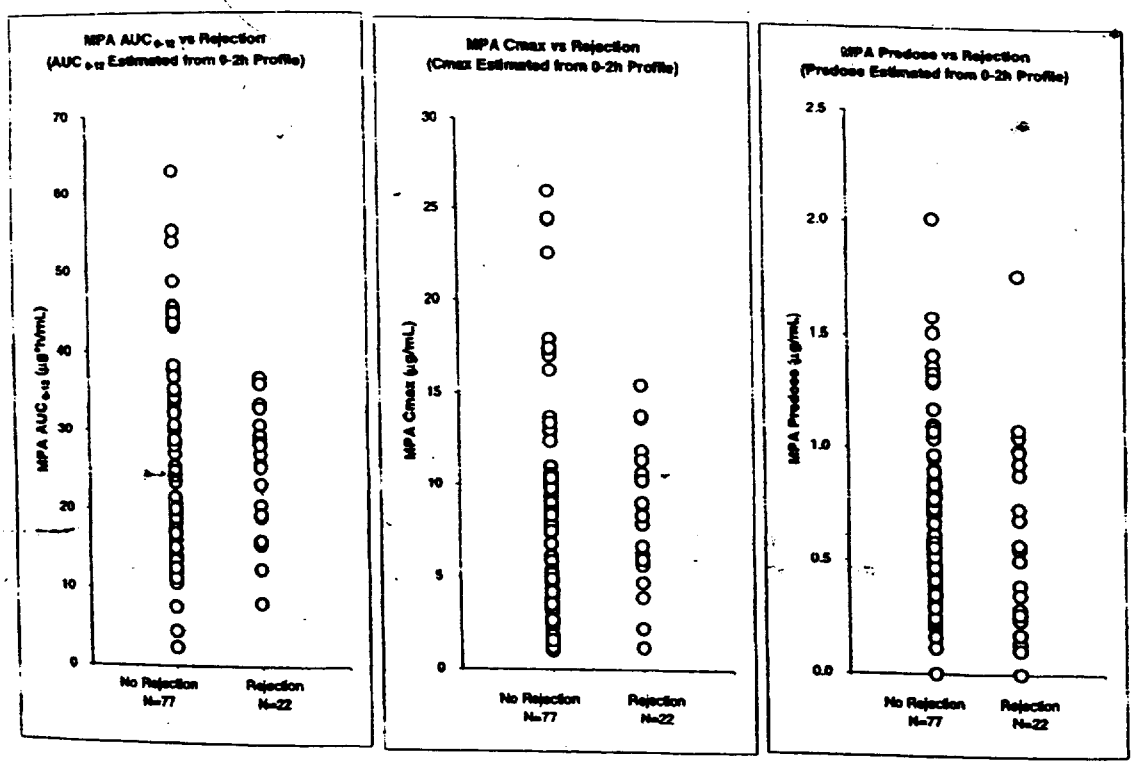
Study Design: This was a single center, open-label, two period crossover study in 12 patients. The patients for this study were stable (at least 6 months) hepatic transplant patients between the ages of 18 and 55 years with hemoglobin concentration greater than 10 g/dL. The patients dose regimen was required to be stable for at least 2 weeks prior to the study. The duration of the study was approximately 2 weeks. Patients who had received cholestyramine and other cholesterol binding agents were excluded from the study. Each patient continued on his or her usual [redacted] dose which was to remain unchanged during the study. Treatment A consisted of [redacted] alone administered in the AM and PM. Treatment B consisted of a combination of [redacted] and MMF. On the pharmacokinetic assessment day (days 7 and 14) for [redacted] alone and [redacted] plus MMF treatment phase, the morning dose was taken after a 12 hour overnight fast. The evening dose was taken after the 12-hour blood sample. MMF dose was 1.5 gm P.O. bid [redacted] dose was the patient's usual maintenance therapy. Pre-dose blood samples were drawn for the assay [redacted] and its metabolites M-I and M-II, in whole blood and for the MMF metabolites MPA and MPAG in plasma. Blood samples for [redacted] on days 7 and 8 in phase 1 and on days 14 and 15 at baseline (immediately before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 12.5, 13, 13.5, 14, 15, 16, 20, and 24 hours after dosing. Blood samples for

Relationship between Rejection and MPA Pharmacokinetic Parameters in MYCS2646, in Patients Receiving 1.5 g MMF bid Orally, using Mini-Profiles

	MPA AUC(0-12h) (µg•h/mL)		MPA Cmax (µg/mL)		MPA Predose Concentration (µg/mL)	
	Rejection	No-Rejection	Rejection	No-Rejection	Rejection	No-Rejection
Mean	25.5	24.9	7.85	8.01	0.670	0.623
Median	23.9	26.1	5.88	8.18	0.601	0.653
Std. Dev.	11.9	7.55	5.92	4.03	0.396	0.434
Min.	2.32	7.97	1.01	1.20	BLQ	BLQ
Max.	62.8	36.7	26.0	15.5	2.01	1.76
N	77	22	77	22	77	22

Note: In this group of patients 11 patients were on less then 1.5 g bid (500 mg [2 – no rejection, 1-rejection], 750 mg [1 – no rejection], 1 g [5- no rejection, 2 – rejection]).
11 patients were excluded because they rejected before the PK sampling day

Relationship between Rejection and MPA AUC(0-12h) or MPA C_{max} or MPA C_{min} at Day 14



analysis of MPA and MPAG levels were collected at baseline and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after dosing.

Analytical Method:

The following tables provide the mean pharmacokinetic parameters for and its major metabolite after administration of and + MMF.

Mean FK506 Computed Pharmacokinetic Parameter

Parameter	Treatment A	Treatment B
	Mean ± SD (n=12)	
AUC(0-24) (ng*h/mL)	151 ± 70.0	180 ± 71.5
Cmax (ng/mL)	11.04 ± 5.04	11.7 ± 4.57
Cmin (ng/mL)	5.24 ± 2.82	5.93 ± 2.89
Tmax (h)	6.41 ± 6.42	3.28 ± 3.18

Treatment A – Patient received only the assigned regimen of

Treatment B – Patient received 3 gm per day (1.5 g BID) of mycophenolate mofetil for 7 days in addition to the assigned regimen of

FK506 Computed Parameter Confidence Interval Summary (Log Transformed Scale)

		90% Confidence Interval		95% Confidence Interval	
Computed Parameter	Ratio (B/A)	Lower Limit	Upper Limit	Lower Limit	Upper Limit
AUC(0-24)	128.2%	103.6%	158.7%	98.6%	166.7%
Cmax	114.1%	94.6%	137.7%	90.6%	143.7%
Cmin	121.4%	103.5%	142.5%	99.7%	147.9%

Mean Metabolite (M-I) Computed Pharmacokinetic Parameters

Parameter	Treatment A	Treatment B
	Mean ± SD (n=10)	
AUC(0-24) (ng*h/mL)	31.6 ± 23.7	21.4 ± 19.4
Cmax (ng/mL)	4.32 ± 2.41	2.73 ± 1.16
Cmin (ng/mL)	0.632 ± 0.716	0.317 ± 0.575
Tmax (h)	4.50 ± 5.28	2.57 ± 1.08

Treatment A – Patient received only the assigned regimen of

Treatment B – Patient received 3 gm per day (1.5 g BID) of mycophenolate mofetil for 7 days in addition to the assigned regimen of

Computed Parameter Confidence Interval Summary Log Transformed Scale (M-I)

		90% Confidence Interval		95% Confidence Interval	
Computed Parameter	Ratio (B/A)	Lower Limit	Upper Limit	Lower Limit	Upper Limit
AUC(0-24)	71.1%	55.7%	90.7%	52.5%	96.2%
Cmax	74.6%	65.0%	85.7%	62.9%	88.5%
Cmin	83.4%	18.8%	370.0%	4.2%	1672.5%

AUC, Cmax and Cmin of [redacted] were about 28%, 14% and 21%, respectively higher when [redacted] was given alone was compared to [redacted] plus MMF administration. Ln AUC and Ln Cmax did not meet the 90% CI (80% - 125%) for assessing similarity in systemic exposure for this type of study. There was high variability in the data, especially in Cmin. The 90% confidence interval (CI) indicate M-I AUC, Cmax and Cmin after administration of [redacted] alone and in combination with MMF are significantly different.

The following table provides the pharmacokinetic parameters for MPA and MPAG after multiple dose administration of [redacted] plus MMF.

MPA and MPAG Computed Pharmacokinetic Parameters after Multiple Dose Administration of [redacted] plus MMF

Parameter	MPA	MPAG
	Mean ± SD (n=12)	Mean ± SD (n=12)
AUC(0-12h) (μg*h/mL)	59.3 ± 20.3	624 ± 268
Cmax (μg/mL)	19.2 ± 8.94	77.6 ± 29.6
Clearance (L/min)	0.353 ± 0.139	0.0379 ± 0.0238
Tmax (h)	1.58 ± 0.726	2.93 ± 1.18

MMF was not administered alone, hence the effect of [redacted] on MPA and MPAG concentrations could not be evaluated in this study.

Conclusion: The systemic exposure of [redacted] when administered alone was not comparable to that when [redacted] was given in the presence of MMF using 90% CI (80% - 125%) criteria for Ln Cmax and Ln AUC. However, the applicant stated that the difference in [redacted] concentrations after co-administration of [redacted] plus MMF would not be clinically significant in terms of efficacy and safety. The applicant stated that plasma [redacted] concentrations is routinely used to adjust [redacted] dosing. The applicant stated that [redacted] was well tolerated in this study.

Reviewer's comments: The study did not evaluate the effect of [redacted] on MPA and MPAG concentrations after coadministration of [redacted] and MMF. There was large variability in the [redacted] concentrations reported. However, since [redacted] therapy is concentration controlled, individualization of [redacted] concentration to maintain it within a therapeutic range is possible. The safety implications of co-administering MMF with [redacted] is not known.

Effect of Race on the Pharmacokinetics of MPA and MPAG in Hepatic Transplant Patients

In the renal transplant patients, it was observed that there was a trend for black patients to have lower AUC(0-12h) compared to Caucasian patients. There was insufficient number of black patients in the pivotal clinical trial to examine the effect of race on the pharmacokinetics of MPA and MPAG in hepatic transplant patients.

Indications and Usage (Per draft label)

Renal, Cardiac and Hepatic Transplant: Cellcept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. Cellcept should be used concomitantly with cyclosporine and corticosteroids.

Cellcept Intravenous is an alternative dosage form to Cellcept capsules, tablets and oral suspension. Cellcept intravenous should be administered within 24 hours following transplantation. Cellcept Intravenous can be administered for up to 14 days; patients should be switched to oral Cellcept as soon as they can tolerate oral medication.

General Conclusions

1) There was no significant difference in the pharmacokinetics of MPA when intravenous administration is compared to first oral administration.

2) There was significant difference in systemic exposure (AUC, Cmax) of MPA when exposures after 1st oral dose are compared to the exposures after 6-month oral dose

3) MPAG pharmacokinetics was significantly different after IV administration and 1st oral dose. MPAG pharmacokinetics was significantly different when 1st oral dose and 6 month oral dosing pharmacokinetics are compared.

4) MPA concentrations in hepatic transplant patients tended to increase after oral dosing and appear to stabilize at or after 6 months.

5) Females tended to have numerically lower AUC(0-12h) than males in the pivotal clinical study but there were fewer females (6) than males (16) who had full pharmacokinetic profiles.

6) PK/PD relationship was not studied. However, exploratory evaluation of AUC, Cmax and predose MPA concentration from a subset of patients in the pivotal clinical trial did not suggest a correlation between these parameters and biopsy proven rejection.

7) There was insufficient African American patients in the studies to determine whether the pharmacokineitcs of MPA in African American hepatic transplant patients differs from other patient populations. Such an observation was suggested for renal transplant patients.

Labeling Comments

The following are the recommendations/changes in the clinical pharmacology sections of the proposed label.

Pharmacokinetics in Healthy Volunteers, Renal, Cardiac and Hepatic Transplant Patients:

Shown below are the mean (± SD) pharmacokinetic parameters for MPA following the administration of mycophenolate mofetil given as single doses to healthy volunteers and multiple doses to renal, cardiac and hepatic transplant patients. In the early posttrasnplant period (<40 days posttransplant), renal, cardiac and hepatic transplant patients had mean MPA AUC approximately 20% to 41% lower and mean Cmax approximately 32% to 44% lower compared to the late transplant period (3 – 6 months posttransplant)

Mean MPA AUC values following administration of 1 g bid intravenous mycophenolate mofetil over 2 hours to renal transplant patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate posttransplant phase. In hepatic transplant patients, administration of 1 g bid intravenous Cellcept followed by 1.5 g bid oral Cellcept resulted in mean MPA AUC values similar to those found in renal transplant patients administered 1 g Cellcept bid

Table Starting on Page 7.

Under Hepatic Transplant Patients (bid dosing) Section (on Page 8):

The following changes are recommended:

1) Please delete the 3-month data from the table. This will be consistent with the descriptions for early and late in renal and cardiac transplant patients. Concentrations of MPA after oral administration to hepatic transplant patients also appear to stabilize after 6-months of therapy.

2) For the Late (> 6 months) data, please use the following values from the pivotal study (MYCS 2646) for patients who only received 1.5 g bid orally.

AUC (µg*h/mL):	49.3 ± 14.8 (n = 6)
Cmax (µg/mL):	19.3 ± 11.7 (n = 6)
Tmax (h):	1.54 ± 0.51 (n = 6)

Tacrolimus- Mycophenolate mofetil Drug Interaction:

After discussions with the reviewing medical officers, it is recommended that the information on Tacrolimus-Mycophenolate mofetil interaction should not be included in the label. There appears to be little reason to include this information from a safety standpoint, and since clinical studies (Phase III) have not been conducted, the FDA does not wish to give implicit approval of this combination before it has been studied.

General Comments

The applicant provided adequate information on the pharmacokinetics of MPA and MPAG in hepatic transplant patients. The selection of the dose was based on matching the AUC(0-12h) values in hepatic to that observed in renal transplant patients. But since a PK/PD relationship between AUC and biopsy proven rejection was not studied in hepatic transplant patients, reliance solely on AUCs observed in renal transplant patients to select dosing schemes for hepatic transplant patients might not be appropriate. A pivotal safety and efficacy study was submitted in support of this application. It is suggested that the applicant continue to explore in future studies whether a PK/PD relationship exists between an appropriate pharmacodynamic endpoint (e.g. biopsy proven rejection) and AUC(0-12h), Cmax or Cmin in hepatic transplant patients.

Recommendation

The pharmacokinetic studies submitted to the Human Pharmacokinetics and Bioavailability section of NDA 50,722 (SE1-005) to fulfill sections 320 and 201.5 of 21 CFR are acceptable and support a recommendation for approval.

CPB Briefing held on 7/13/200. Attendees: Drs. John Lazor, Arzu Selen, Frank Pelsor, Dan Wang, Funmi Ajayi and Kofi Kumi.

/S/ 7/18/2000

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/S/

Concurrence__ 7/18/00

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DPE3/OCPB

NDA 50,722 (SE1-005) (original)

CC	HFD-590	/Division Files
		/MO/J Korvick
		/MO/R Roca
		/PM/M Bacho
	HFD-340	/Viswanathan
	HFD-880	/TLDPEIII/F Ajayi
		/DPEIII/ K Kumi
		/DPEIII Drug Files
	CDR	/B Murphy