CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 50758

CHEMISTRY REVIEW(S)

AUG 11 1998

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS—HFD-590

Review of Chemistry, Manufacturing and Controls Section

NDA #: 50-758 (formerly NDA 20-842)
CHEMISTRY REVIEW #: 1 **REVIEW COMPLETED:** August 10, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	August 29, 1997	September 2, 1997	September 10, 1997
BC (re: EA)	January 6, 1998	January 7, 1998	January 15, 1998
BC (stability update)	January 30, 1998	February 2, 1998	February 4, 1998
BC	February 20, 1998	February 23, 1998	March 2, 1998
BC	May 22, 1998	May 27, 1998	June 5, 1998
NC	June 8, 1998	June 10, 1998	-
BC	June 16, 1998	June 18, 1998	June 29, 1998

NAME/ADDRESS OF SPONSOR: Syntex (U.S.A.) Inc.
3401 Hillview Avenue
Palo Alto, California 94303

DRUG PRODUCT NAME:
Proprietary: CellCept Intravenous
Established Name: mycophenolate mofetil hydrochloride for injection

CHEM. TYPE/THER. CLASS: 3S
DRUG CLASS: 5010400
PHARMACOLOGICAL CATEGORY: Immunosuppressant

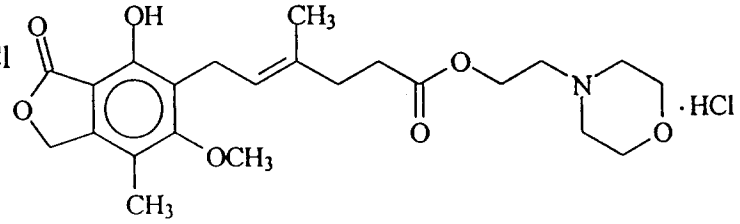
INDICATION: Prophylaxis of transplant rejection and increase patient and graft survival in patients receiving allogenic renal and cardiac transplants

DOSAGE FORM/STRENGTH: Powder for solution, equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt

ROUTE OF ADMINISTRATION: Intravenous infusion

CHEMICAL NAME(S)/STRUCTURAL FORMULA:
4-Hexenoic acid, 6-(1,3-dihydro-4-hydoxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl)-, 2-(4-morpholinyl)ethyl ester, (E)-, hydrochloride

CAS Registry: 128794-94-5
Molecular Formula: $C_{23}H_{31}NO_7 \cdot HCl$
Formula Weight: 469.96



Other chemical names for the hydrochloride salt:
1) 2-Morpholinoethyl (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-hexenoate hydrochloride
2) 2-Morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzo-furanyl)-4-methyl-4-hexenoate hydrochloride

Free base (mycophenolate mofetil): code name RS-61443; $C_{23}H_{31}NO_7$; mw 433.50; CAS 115007-34-6.

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS:

N50-722/SCS-001 Drug substance manufacturing supplement; AP 6/12/97

Memoranda of Telephone Conversations February 19, 1998; May 8, 1998; May 12, 1998; May 13, 1998; May 19, 1998; June 16, 1998.

CONSULT REVIEWS:

Microbiology Review of Sterile Process: P. Hughes, HFD-160; January 23, 1998
Review of Response to Microbiology Deficiencies: P. Hughes, HFD-160; February 12, 1998

CGMP STATUS

The Office of Compliance reports that all facilities involved in the manufacture of CellCept Intravenous have acceptable cGMP status

LABELING

At our request several minor revisions have been made to the labeling (package insert, carton and vial label). The draft labeling as submitted on July 20, 1998, is acceptable. The final printed labeling should be identical to this draft.

ENVIRONMENTAL ASSESSMENT

A categorical exclusion has been claimed in accordance with the revised regulations published in the Federal Register on July 29, 1997 (21 CFR 25.31(b)). The categorical exclusion is acceptable.

CONCLUSIONS & RECOMMENDATIONS:

Additional specifications assure the suitability of the drug substance for use in the intravenous product.

The applicant has addressed the few issues raised during the review of this application, including revision of the drug product specifications, commercial stability protocol and labeling. The chemistry, manufacturing and controls, as amended, are adequate to assure the identity, quality, purity and strength of the drug product.

From the chemist's perspective, this New Drug Application for CellCept Intravenous is approvable as amended.

/S/ 8/10/98

Mark R. Seggel, Review Chemist

Concurrence:
HFD-830/CChen
HFD-590/NSchmuff /S/ 8/11/98

cc:

Orig. NDA	HFD-590/MDempsey	
HFD-590/Div. File	HFD-590/KKumi	
HFD-590/NSchmuff	HFD-590/MSeggel	
HFD-590/JKorvick	HFD-830/CChen	File: N50-758.cr1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 50758

MICROBIOLOGY REVIEW(S)

590 Dempsey

FEB 19 1998

REVIEW TO HFD-590
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGY REVIEW OF NDA
February 12, 1998

A. 1. NDA 50-758

PRODUCT NAME: CellCept Intravenous Powder for Solution
Mycophenolate Mofetil Hydrochloride Injection Powder for Solution

APPLICANT: HOFFMANN LA ROCHE
Manufacturing Site: Parke-Davis
870 Parkdale Road
Rochester, MI 48307

B. 1. DOSAGE FORM: Mycophenolate mofetil hydrochloride sterile lyophilized powder for infusion (500 mg/vial) after reconstitution.

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2. METHOD(S) OF STERILIZATION:

3. PHARMACOLOGICAL CATEGORY/PRINCIPAL INDICATION:
Transplantation recipients

APPEARS THIS WAY
ON ORIGINAL

C. 1. DATE OF AMENDMENT # 1:

APPEARS THIS WAY
ON ORIGINAL

2. ASSIGNED FOR REVIEW: February 11, 1998

D. REMARKS: This amendment addresses microbiology deficiencies found in the original NDA submission.

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ON ORIGINAL

E. CONCLUSIONS: The NDA 50-758 for CellCept Intravenous (Mycophenolate Mofetil HCL) Powder-500 mg is recommended for approval from the standpoint of product quality microbiology.

/S/

APPEARS THIS WAY
ON ORIGINAL

Patricia F. Hughes, Ph.D.
Review Microbiologist

cc.: Original NDA 50-758
HFD-160/Division File
HFD- 160/PFHughes
HFD-590/MDempsey
HFD-590/DivFiles
Drafted by PF Hughes, 2/12/98
R/D Initialed by PH Cooney

/S/

2-19-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 50758

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUL 21 1998

Clinical Pharmacology/Biopharmaceutics Review

NDA:50,758 **Submission Dates**: 9/2/97, 3/11/98

Generic Name, Strength and Formulation: Mycophenolate Mofetil Hydrochloride Injection, 500 mg Powder for reconstitution

Brand Name: Cellcept(R) **Date Assigned:** 9/12/97

Applicant: Roche (Syntex USA, Inc) **Final Review:** 7/21/98

Submission Code: 3S **Reviewer:** Kofi A. Kumi, Ph.D.

SYNOPSIS

The applicant submitted a new drug application (NDA) for intravenous (IV) formulation of Mycophenolate Mofetil (MMF, Cellcept) intended to be an alternative form for use where clinical condition of patients prevents the oral (PO) administration of drugs. MMF is available commercially as 250 mg capsules and 500 mg tablets. MMF is approved (NDA 50,722 and 50,722-SE1) for use in the prevention of acute allograft rejection following renal and cardiac transplantation. In this application, the sponsor submitted 9 studies using the IV formulation. Two of the studies conducted in hepatic transplant patients were not reviewed since the applicant is not currently seeking the use of the IV formulation in hepatic transplant patients. None of the studies using the IV formulation was conducted in cardiac transplant patients. In three pivotal studies in renal transplant patients, multiple dose studies were conducted in the immediate post transplant period and the sequence of administration of the formulations was IV followed by PO as is expected to be the case in clinical practice. Four of the studies (one interim report) were originally submitted to NDA 50,722.

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The pharmacologic activity of MMF resides in the hydrolytic product, mycophenolic acid (MPA). 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) after oral administration. In NDA 50,722, it was determined that patients with severe alcoholic cirrhosis rapidly metabolized MMF to MPA. The development strategy of the IV formulation was to show that the area under the concentration time curve (AUC) of MPA after IV and PO administration of MMF were similar.

In the pivotal pharmacokinetic study (MYCS 2734) using the proposed dosing regimen of 1gm MMF twice daily (BID) and the approved oral regimen of 1 gm BID, the mean pharmacokinetic parameters for MPA computed on day 5 after multiple IV dosing followed by PO administration of MMF on day 6 (first day of PO dosing) are contained in the following table.

Mean Pharmacokinetic Parameters of MPA

Parameter	IV	Oral
	Mean ± SD MPA (n= 31)	
AUC (0-12) μg*hr/mL	40.8 ± 11.4	32.9 ± 15.0
Cmax (μg/mL)	12.0 ± 3.82	10.7 ± 4.83
Tmax (hr)	1.58 ± 0.46	1.33 ± 1.05

The mean exposure (AUC) of MPA on day 5 of IV dosing was statistically significantly higher (about 24% higher, $p<0.001$) than that observed on day 6 after oral administration, but the maximum concentration (Cmax) and Tmax were not statistically significantly different ($p=0.252$); however, there was a trend towards higher Cmax after IV compared to oral administration.

The mean extent of MPA exposure (AUC = 40.8 ± 11.4μg*hr/mL) on day 5 after administration of MMF 1 gm twice a day (BID) intravenously was similar to that observed in renal transplants (n=20) on day 5 receiving 1.5 gm orally BID (AUC = 39.7 ±21.2 μg*hr/mL; NDA 50,722 study 1866) and cardiac transplant patients (n=9) on day 7 after administration of MMF 1.5 gm orally (AUC = 43.3 ± 20.8 μg*hr/mL; NDA 50,722 SE1-002). The mean AUC after administration of 1 gm BID orally to patients (n=27) during the early period (< 40 days) after renal transplantation was 27.3 μg*hr/mL. However, it is less than the mean exposure reported for stable renal transplant (≥3 months post transplant) patients (AUC= 65.3 μg*hr/mL) and stable cardiac transplant patients (mean AUC= 54.1 ± 20.4 μg*hr/mL) who received MMF 1.5 gm BID orally (NDA 50,722 and 50,722SE1-002).

The mean AUC, Cmax and Tmax of MPAG on day 5 after IV administration for 5 days followed by oral administration on day 6 (1st day of PO dosing) is provided in the following table.

Mean Pharmacokinetic Parameters of MPAG

Parameter	IV	Oral
	Mean ± SD MPAG (n= 31)	
AUC (0-12) μg*hr/mL	720 ± 316	746 ± 302
Cmax (μg/mL)	74.6 ± 27.3	80.2 ± 27.5
Tmax (hr)	3.42 ± 2.03	3.61 ± 2.73

There was no statistically significant differences in the AUC, Cmax and Tmax of MPAG after IV compared to oral administration.

MMF concentrations were not measured in this pivotal study (MYCS 2734). However, MMF concentration was measured in a supportive study (MYC061). The mean±SD MMF concentration (dose: 1.5 gm BID) on day 7 for 1 and 3 hour infusions were 2.50 ± 0.877 and 4.45 ± 6.07 μg/mL, respectively

In a discussion with the reviewing pharmacologist, the concentration of MMF observed is not expected to be clinically relevant.

Drug Interaction: No new information on the potential for drug interaction was submitted in this application. Drug interaction studies submitted to NDA 50,722 are cross referenced in this application.

Gender, Ethnicity and Age: There were insufficient numbers of patients in any of the studies to adequately evaluate the influence of gender, ethnicity or age on the pharmcokinetic parameters after IV administration of MMF.

Proposed Indication (From Draft Label): Renal and Cardiac Transplant: Cellcept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants and in patients receiving allogeneic cardiac transplants. Cellcept should be used concomitantly with cyclosporine and corticosteroids.
Cellcept Intravenous is an alternative dosage form to Cellcept capsules and tablets. Cellcept Intravenous should be administered within 24 hours following transplantation for up to 14 days. Patients should be switched to oral Cellcept as soon as they can tolerate oral medication.

COMMENTS

There were no studies conducted in cardiac transplant patients using the IV formulation. However, because of the similarities in the pharmacokinetics of MPA and MPAG in cardiac and renal transplant patients after administration of oral MMF, it is acceptable to use the intravenous formulation in cardiac transplant patients. A dose of 1.5 gm, infused over a period not less than 2 hours, twice daily is recommended.

There was insufficient patient numbers to adequately evaluate gender differences in the pharmacokinetics of MMF after IV administration. However, there was a suggestion of higher AUC in females after IV administration in study 2734. This observation was not evident after oral administration. It is recommended that the applicant evaluate in planned future studies whether there is a gender difference in the pharmacokinetics of MPA after IV administration.

In general, the applicant is encouraged to continue exploring whether there are ethnic and gender differences in the pharmacokinetics of MPA and MPAG after administration of MMF.

RECOMMENDATION

The pharmacokinetic studies submitted to the Human Pharmacokinetics and Bioavailability section of NDA 50,758 to fulfill sections 320 and 201.5 of 21 CFR are acceptable and support a recommendation for approval.

/S/ 7/21/98

Kofi A. Kumi, Ph.D.
Pharmacokinetics Reviewer
HFD 590 Section
Division of Pharmaceutical Evaluation III

/S/

Concurrence: 7/21/98

Funmi Ajayi, Ph.D.
Acting Team Leader
HFD 590 Section
Division of Pharmaceutical Evaluation III

NDA 50,758 (original)

CC	HFD-590	Division Files
		/MO/MCavaille-Coll
		/MO/JKorvick
		/PM/MDempsey
	HFD-340	/Viswanathan
	HFD-880	/TLDPEIII/FAjayi
		/DPEIII/KKumi
		/DPEIII Drug Files ✓
	CDR	/Attn: Murphy ✓

file: WP6.1/data/kumiwp/cellcept/IV/overal3

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REVIEW

Background

The new drug application (NDA) was submitted for approval for use of intravenous (IV) mycophenolate mofetil (MMF) for the prophylaxis of organ rejection in renal and cardiac transplant patients. The IV formulation of MMF is intended to provide an alternative dosage form for use, especially during the early transplant period, where the clinical condition of patients prevents the oral administration of drugs. MMF is used in combination with corticosteroids and cyclosporine. The pharmacokinetics of MMF, the prodrug, mycophenolic acid (MPA), the pharmacologically active metabolite of MMF and MPA glucuronide (MPAG), the major metabolite excreted in the urine, were evaluated after IV administration. There were 3 pivotal studies in which the pharmacokinetics of MMF, MPA and MPAG after both IV and oral administration were evaluated in renal transplant patients. The pharmacokinetics of MMF, MPA and MPAG after IV administration of MMF were also evaluated in healthy volunteers, patients with impaired liver and renal function and hepatic transplant patients. Individual data and Appendices are on file in the Division of Pharmaceutical Evaluation III

MMF is the morpholino-ethyl ester pro-drug for mycophenolic acid (MPA). MMF is hydrolyzed to MPA, which is a selective, noncompetitive and reversible inhibitor of inosine monophosphate, a critical enzyme in the *de novo* pathway for purine biosynthesis which blocks the proliferation of both T and B lymphocytes. MMF was demonstrated to be an effective immunosuppressive agent for the prevention of acute rejection in renal and cardiac allografts in a variety of species. From the oral application (NDA 50,722), the mean absolute bioavailability after oral administration is reported to be 94%. MPA undergoes conversion to an inactive glucuronide (MPAG) which is eventually excreted in urine. MPAG is excreted in bile and is believed to be deglucuronidated in the colon and thereby undergoes enterohepatic recycling (as MPA). This finding was based on the observation of a secondary post administration and a 40% reduction in the AUC of MPA when MMF was coadministered with cholestyramine. Orally administered radio-labeled MMF resulted in complete recovery of the administered dose (93% in the urine and 6% in feces). Most of an administered dose is excreted in the urine as MPAG; less than 1% is reported excreted in the urine as MPA. MMF is reported not to be detected in the plasma after oral administration. The mean ± SD apparent half-life of MPA is 17.9 ± 6.5 hours after oral administration. MPA and MPAG are extensively bound (97% for MPA and 82% for MPAG) to plasma proteins, mainly serum albumin. In renal transplant patients, it was observed that AUC and Cmax were approximately 50% lower in the immediate post transplant period (≤ 40 days) compared to stable renal transplant period (≥ 3 months) or in healthy patients.

Formulation

Ingredients	Composition	
	Weight % in bulk solution	mg/vial in finished product
Mycophenolate mofetil		
Polysorbate 80		

Analytical Method

OVERVIEW OF PHARMACOKINETIC STUDIES

Pivotal Studies: Pharmacokinetics in Renal Transplant Patients

Study MYCS 2734 (P-180194): A 6-Day Open Label Pharmacokinetic Bioavailability Evaluation of Mycophenolic Acid when Switching from Intravenous Mycophenolate Mofetil to Oral Mycophenolate in Renal Transplant Recipients in the Immediate Postoperative Period (Volume 23 page 1)

Background: Mycophenolate mofetil (MMF, Cellcept) an immunosuppressive agent is approved for prophylaxis of organ rejection in patients receiving allogeneic renal transplant. It is currently available for oral administration as 250 mg capsules and 500 mg tablets. Following oral administration, MMF undergoes rapid and extensive absorption and complete presystemic metabolism to mycophenolic acid (MPA), the active metabolite. The sponsor has developed an intravenous (IV) formulation for use in patients who can not tolerate the oral capsules and tablets. In this study, the recommended dosage regimen, I gm infused over 2 hours administered 2 times a day (BID), was evaluated; this was the first study in which the proposed dosing regimen for IV MMF was used.

Objectives: The primary objective of this study was to compare the bioavailability of IV MMF (1gm BID) when switching from an IV infusion (1gm BID over 2 hours) on Day 5 to oral capsules bid, (4 x 250 mg) on Day 6 in the period immediately following transplantation.

Study Design: This study was a multi center, open-label study of renal transplant recipients in the immediate postoperative period. Approximately 45 patients from 8 centers in the USA and Canada participated in this study. Patients enrolled in the study must be able to receive oral medication 6 days post transplant. Patients enrolled were to receive IV MMF for 4.5 days (9 or 10 doses) and oral MMF for 1 day (2 doses). The first 1 gm of IV MMF was administered no later than 24 hours post transplant. The IV study drug was given twice a day through the morning of day 5. The IV solution was infused over 2 hours at a rate of 84 mL/hr. The first blood samples for pharmacokinetic analysis were taken immediately predose (0 mins), 20, 30, 40, 80, 100, 140 and 160 mins and at 3, 4, 6, 8 and 12 hours after AM study drug administration on study days 5 (from start of infusion) and 6. Plasma samples were analyzed for MPA and MPAG concentrations by

The batch and formulation numbers for the IV used in the study are 61443-000-902051 and F61443-094, respectively. The batch and formulation numbers for the oral capsule formulation are 61443-000-1179631 and F61443-051, respectively.

Data Analysis: The pharmacokinetic parameters computed were Cmax, Tmax, AUC(0-12), Cave, Cmin (end-of-dosing interval plasma concentration computed as the mean of zero and 12 hour concentration), Cmax/Cmin, Cmax/Cave and % Fluctuation.

Results: Pharmacokinetic analyses were conducted on 31 of the 45 patients who enrolled in the study. The mean±SD age and weight of these patients were 43.6 ± 12.7 years and 76.9 ± 14.2 kg, respectively. The mean plasma concentration time profiles of MPA are provided in figure 1 on the following page. The mean concentration after IV administration of MMF was higher than after oral administration initially, but the terminal phase of the two profiles were similar. The mean AUC, Cmax and Tmax of MPA on day 5 and 6 after administration of both IV and oral MMF are contained in the table below. Individual pharmacokinetic parameters are contained in Appendix.

Mean Pharmacokinetic Parameters of MPA

Parameter	IV	Oral
	Mean ± SD MPA (n= 31)	
AUC (0-12) μg*hr/mL	40.8 ± 11.4	32.9 ± 15.0
Cmax (μg/mL)	12.0 ± 3.82	10.7 ± 4.83
Tmax (hr)	1.58 ± 0.46	1.33 ± 1.05

MYCS2734
INV: Multiple

Figure 1

Figure 4.3A Mean Plasma Concentrations of MPA versus Time

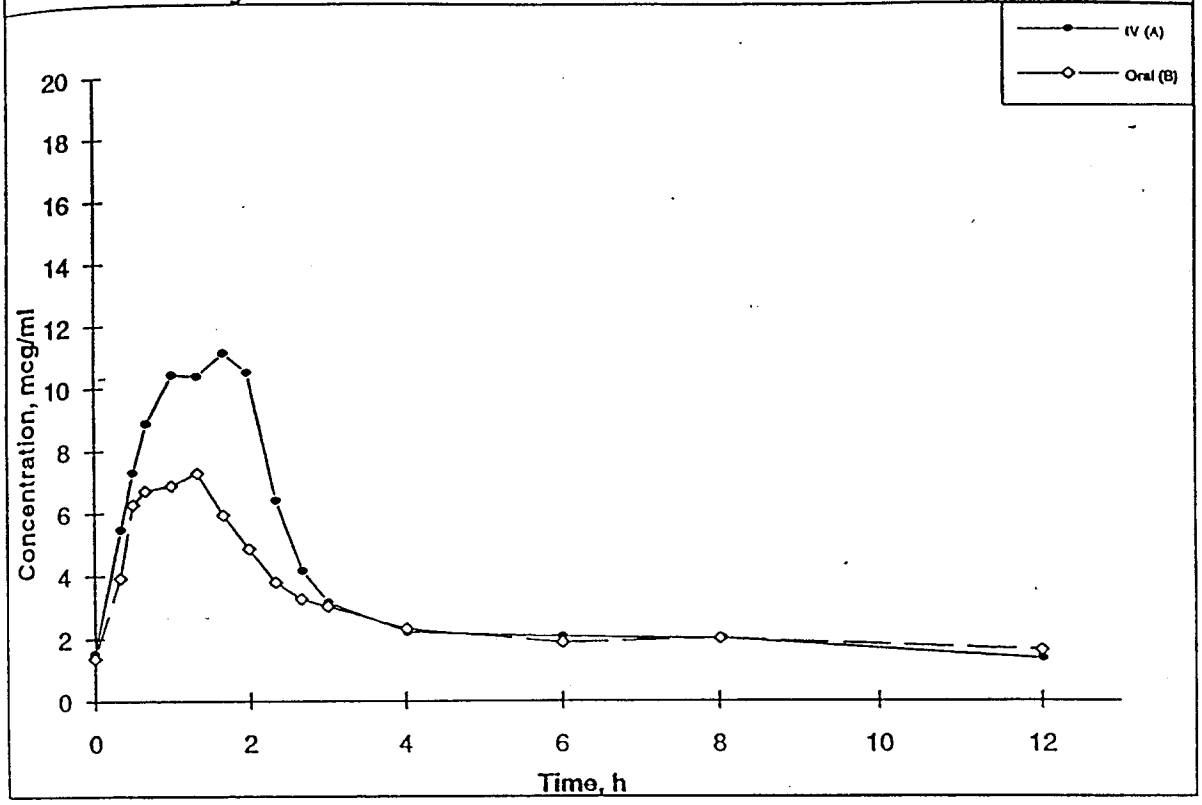
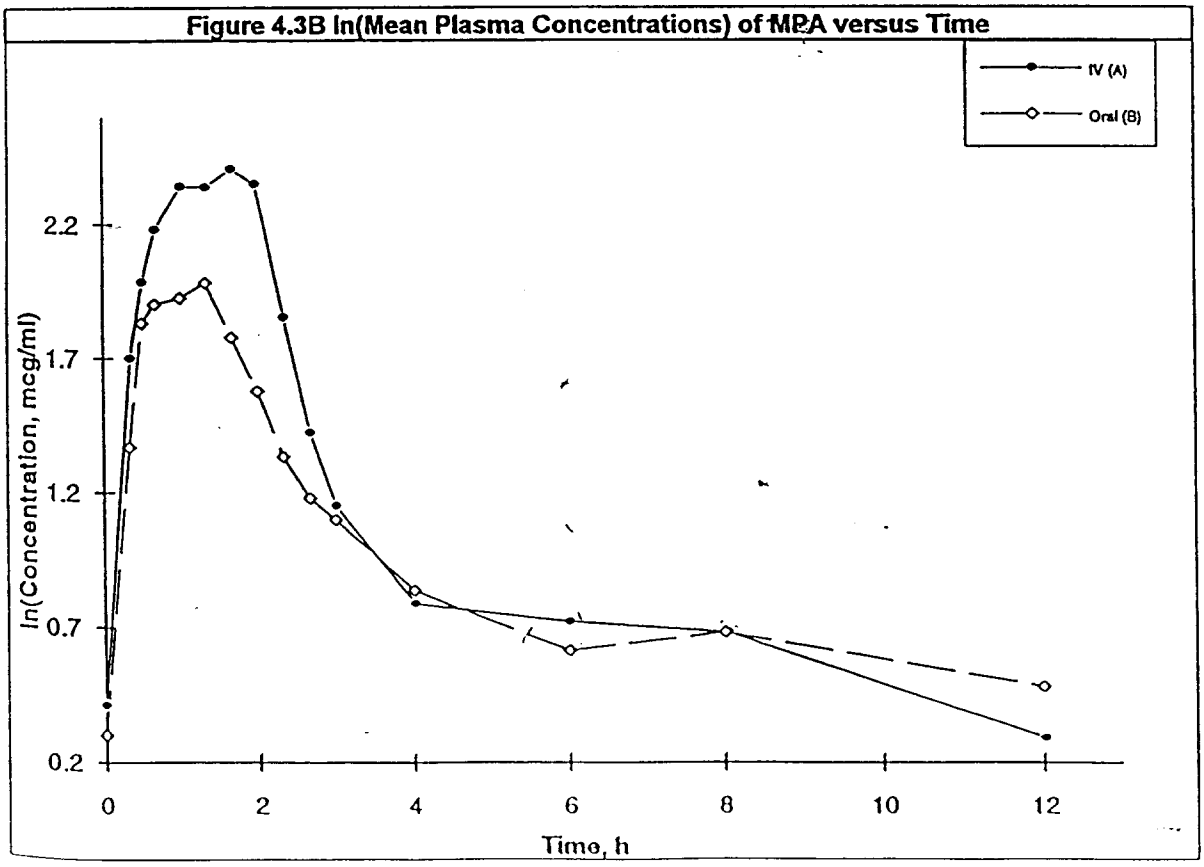


Figure 4.3B ln(Mean Plasma Concentrations) of MPA versus Time



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The mean exposure (AUC) of MPA on day 5 of IV dosing was statistically significantly higher (about 24% higher) than that observed on day 6 after oral administration, but the maximum concentration (Cmax) and Tmax were not statistically significantly different. However, there was a trend towards higher Cmax after IV compared to oral administration. The MPA computed parameter confidence interval summary are provided in the table on the following page. The individual data showed the same general trend of higher AUC of MPA after IV than after oral administration except for 5 patients in which the exposure was similar or higher after oral administration. The variability in the relative AUC (IV vs Oral) was about 36%. One patient had about 127% higher AUC after IV compared to oral administration while at the lower end, a patient had about 32% lower AUC after IV compared to oral administration.

There was no statistically significant difference ($p<0.05$) in Cmax and AUC of MPA when blacks were compared to non-blacks after administration of IV MMF. However, it must be noted that the number of blacks with pharmacokinetic data were relatively smaller (5) than non blacks (26). This observation is in contrast to the trend observed for blacks after oral administration in the previous oral application (NDA 50,722).

There was a significant difference in AUC of MPA when the weight adjusted values for females were compared to males after IV administration of MMF; mean AUC were higher for females compared to males. This significant difference was not observed after oral administration. It must be noted that there were relatively fewer females (8) compared to males (23), hence definite conclusions could not be deduced and the applicant is encouraged to explore this further in other studies.

There was no apparent difference in MPAG profile after IV administration compared to that after oral administration (figure in appendix). The mean AUC, Cmax and Tmax for MPAG after administration of both IV and oral MMF are contained in the following table

Mean Pharmacokinetic Parameters of MPAG

Parameter	IV	Oral
	Mean ± SD MPAG (n= 31)	
AUC (0-12) μg*hr/mL	720 ± 316	746 ± 302
Cmax (μg/mL)	74.6 ± 27.3	80.2 ± 27.5
Tmax (hr)	3.42 ± 2.03	3.61 ± 2.73

There was no statistically significant differences in the AUC, Cmax and Tmax of MPAG after IV compared to oral administration. The mean AUC of MPAG on day 5 appeared smaller after IV administration of MMF to renal patients when compared to that computed for cardiac patients in NDA 50,722/SEI-002, study 1864. Mycophenolic mofetil levels were not determined in this study.

MYCS2734
INV: Multiple

Appendix 4.2
MPA Computed Parameter Confidence Interval Summary
Comparison of IV (A) vs Oral (B)

Untransformed Scale

Computed Parameter	Ratio (A/B)	90% Confidence Lower Limit	90% Confidence Upper Limit	95% Confidence Lower Limit	95% Confidence Upper Limit	Intra CV
AUC 0-12	123.9%	114.5%	133.3%	112.6%	135.2%	19%
Cmax	112.5%	94.4%	130.6%	90.7%	134.3%	40%
Tmax	118.8%	92.7%	144.9%	87.4%	150.2%	55%

Log Transformed Scale

Computed Parameter	Ratio (A/B)	90% Confidence Lower Limit	90% Confidence Upper Limit	95% Confidence Lower Limit	95% Confidence Upper Limit	Intra CV
AUC 0-12	128.7%	118.8%	139.4%	116.8%	141.7%	19%
Cmax	120.1%	101.3%	142.5%	97.8%	147.5%	40%

Formulations:
A = MMF 1 g bid given as an IV infusion over 2 hours.
B = MMF 1 g bid given as capsules (4 x 250mg).

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Conclusion: The extent of exposure of MPA after administration of 1 gm MMF over 2 hours was about 24% higher after IV than oral administration; however, MPAG concentrations were similar. There was no significant difference in Cmax of MPA and MPAG when IV is compared to oral MMF administration. The extent of exposure of MPA after IV administration of 1 gm MMF over 2 hours on day 5 to renal transplant patients was similar to that observed for cardiac patients receiving 1.5 gm MMF orally during the early period (day 7) after transplantation.

Study MRE/MYC061: Open-Label, Randomized Investigation of the Pharmacokinetics of Mycophenolate Mofetil 3 gm per Day Given in Two Divided Doses Orally (PO) or as Intravenous (IV) Infusions of 1 or 3 Hours Duration or as Continuous Infusion to Renal Allograft Recipients for the Prevention of Rejection (Volume 45 page 1)

Background: Intravenous (IV) MMF has been developed to provide early immunosuppression in the immediate post transplant period, when patients may be unable to tolerate oral medication. This study evaluated the pharmacokinetics of mycophenolate mofetil (MMF), mycophenolic acid (MPA) and mycophenolic glucuronide (MPAG) after intravenous administration over different durations followed by oral administration of MMF. The review concentrates on comparisons of the pharmacokinetics after IV and oral administration of different dosing regimens of MMF.

Objectives: The primary objectives of this study were: 1) to determine the effect of different rates and routes of administration of MMF on the pharmacokinetics of MPA and MPAG and 2) to determine the time required to reach steady state for MPA with each dosing regimen.

Design: This was a multi-center, open-label, parallel-group, randomized study in patients receiving a first or second renal allograft. Sixty-two patients participated in the study- forty six provided pharmacokinetic data for analysis. Patients who required induction therapy were excluded from the study. Patients unable to tolerate oral medication on day 8 were withdrawn from the study. Patients were randomized to receive MMF 1.5 gm po twice daily (bid) for 12 weeks, MMF 1.5 gm as 1-hour IV infusion bid for 1 week followed by 1.5 gm orally bid for 11 weeks, MMF 1.5 gm as 3-hour IV infusion bid for 1 week followed by 1.5 gm orally bid for 11 weeks and 3 gm per day as continuous IV infusion for 1 week followed by 1.5 gm orally bid for 11 weeks. Patients randomized to the IV groups received IV medication within 24 hours of surgery; those randomized to the oral group received medication within 48 hours of surgery. MMF was administered with cyclosporine and corticosteroids according to the local institutional standard protocol. Blood samples were taken for pharmacokinetic assessment of MMF, MPA and MPAG; blood sampling schedule is provided in Appendix. Pharmacokinetics of MPA, MPAG were determined on Days 1, 3, 7, 8 and 14. Time to steady state was assessed from predose MPA concentration data from Day 2 through Day 14. A 24-hour urine collection was made during the period starting with blood sampling for the 12-hour pharmacokinetic profile. Each oral dose unit was provided as 6 x 250 mg capsules. Oral Formulation and Lot No. were F61443-079 and CT1145SC1106Q, respectively. IV Formulation and Lot No. were F61443-094 and 61443-000-902051, respectively.

Sample Analysis: The MPA and MPAG concentrations of all collected samples were [illegible] The quantitation limit for MMF in plasma was 0.4 μg/mL. The quantitation limits for MPA in plasma and urine were 0.1 and 2.5 μg/mL, respectively. The quantitation limits for MPAG in plasma and urine were 4.0 and 50 μg/mL, respectively. For all calculations, the MPAG concentration was converted to MPA equivalents by multiplying by the ratio of the molecular weights of MPA to that of MPAG.

Data Analysis: The following pharmacokinetic parameters were determined from the reported plasma and urine concentrations. Cmax, Tmax, Cmin (computed as the mean of the predose and the end of the dosing interval concentrations), Cmax/Cmin, AUC[illegible] Cave (computed as ratio of AUC[illegible], Cmax/Cave, % Fluctuation (100((Cmax-Cmin)/Cave)), urine amount excreted and % RS Excreted (computed as amount excreted/total dose (computed over 24 hours)).

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Results: A summary of MMF plasma results are provided in Appendix. Plasma concentrations of MMF were detected during the IV infusions but were not measured when the infusions were stopped. MMF was not measured during the oral administration.

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The mean plasma concentration time profile for MPA after the various treatment regimens are provided in the Appendix. A graphical comparison of AUC and Cmax of MPA is provided in figure 3 on the following page. The mean Cmax on days 1 and 7 showed the expected variation with infusion rate with a tendency to increase inversely with infusion duration. The mean AUC, Cmax and Tmax of MPA after administration of the various treatments are provided in the following tables

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Mean AUC(0-12) of MPA

Day of Treatment	Oral Group	1 hr IV Group	3 hr IV Group	24 cont. IV Grp
	Mean ± SD (n)			
1	31.3 ± 15.2 (13)	31.6 ± 10.0 (15)	30.1 ± 10.5 (13)	31.4 ± 7.84 (13)
7	35.6 ± 12.5 (13)	32.3 ± 5.87 (10)	31.7 ± 7.97 (11)	29.3 ± 6.11 (14)
8	34.2 ± 13.0 (13)	29.5 ± 6.86 (10)	30.7 ± 7.97 (10)	37.7 ± 28.8 (13)
14	39.0 ± 15.3 (12)	31.5 ± 12.6 (10)	35.6 ± 10.2 (11)	43.6 ± 15.0 (14)

Oral Group: 1.5 gm MMF po bid.
1 hr IV Group: 1.5 gm bid infused over 1 hr for 7 days followed with 1.5 gm po bid
3 hr IV Group: 1.5 gm bid infused over 3 hr for 7 days followed with 1.5 gm po bid
24 hr IV Group: 1.5 gm continuous infusion for 7 days followed with 1.5 gm po bid

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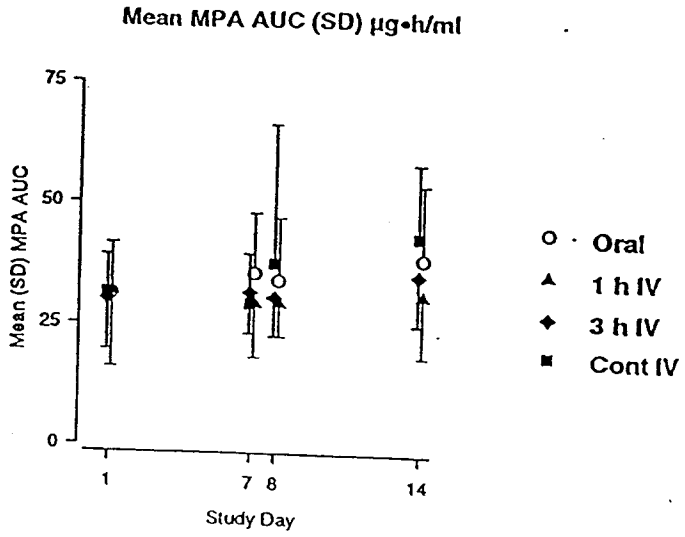
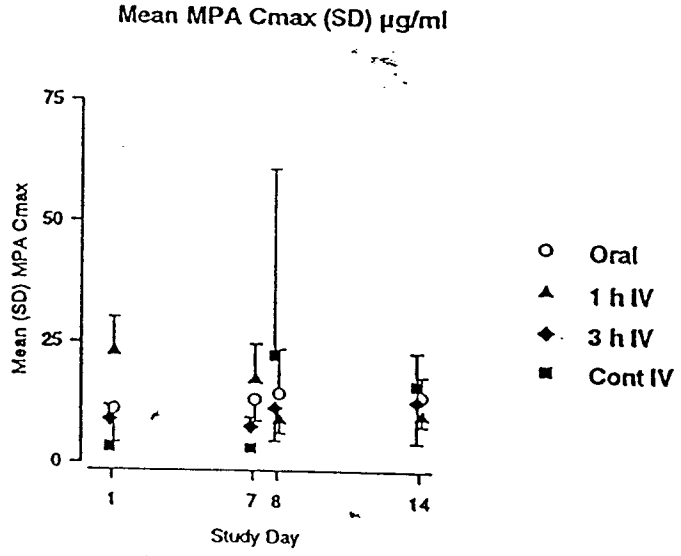
Figure 3





#13

Mean Cmax of MPA

Day of Treatment	Oral Group	1 hr IV Group	3 hr IV Group	24 cont. IV Grp
	Mean ± SD (n)			
1	11.2 ± 6.93 (13)	22.9 ± 7.26 (15)	8.91 ± 2.96 (13)	3.24 ± 0.96 (13)
7	13.2 ± 4.50 (13)	18.8 ± 5.90 (10)	7.58 ± 1.98 (11)	3.14 ± .78 (14)
8	14.4 ±9.16 (13)	8.98 ± 2.77 (10)	11.5 ± 6.94 (10)	22.3 ± 38.6 (13)
14	13.9 ± 4.25 (12)	9.91 ± 2.05 (10)	12.9 ± 8.48 (11)	16.2 ± 6.95 (14)

Oral Group: 1.5 gm MMF po bid.
1 hr IV Group: 1.5 gm bid infused over 1 hr for 7 days followed with 1.5 gm po bid
3 hr IV Group: 1.5 gm bid infused over 3 hr for 7 days followed with 1.5 gm po bid
24 hr IV Group: 1.5 gm continuous infusion for 7 days followed with 1.5 gm po bid

Mean Tmax of MPA

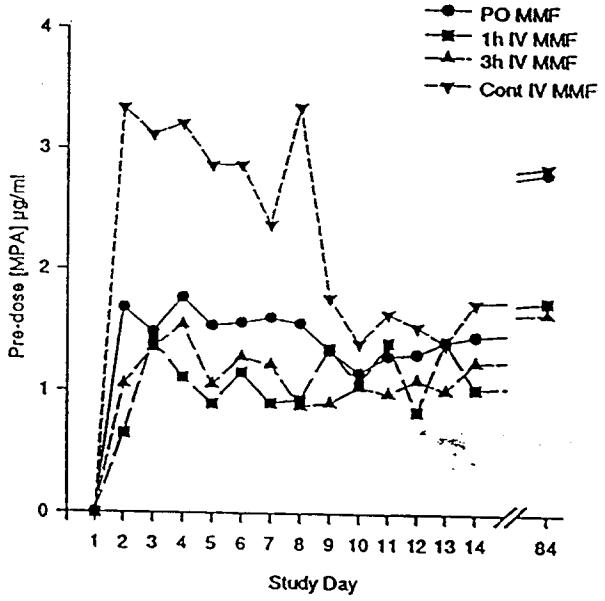
Day of Treatment	Oral Group	1 hr IV Group	3 hr IV Group	24 cont. IV Grp
	Mean ± SD (n)			
1	2.03 ± 3.09 (13)	0.93 ± 0.18 (15)	2.12 ± 1.08 (13)	7.69 ± 4.29 (13)
7	0.94 ± 0.52 (13)	0.90 ± 0.16 (10)	1.90 ± 1.04 (11)	4.50 ± 4.51 (14)
8	0.84 ± 0.37 (13)	1.65 ± 0.91 (10)	1.29 ± 0.76 (10)	1.19 ± 0.69 (13)
14	1.32 ± 0.43 (12)	1.51 ± 0.59 (10)	1.40 ± 1.07 (11)	1.42 ± 0.76 (14)

Oral Group: 1.5 gm MMF po bid.
1 hr IV Group: 1.5 gm bid infused over 1 hr for 7 days followed with 1.5 gm po bid
3 hr IV Group: 1.5 gm bid infused over 3 hr for 7 days followed with 1.5 gm po bid
24 hr IV Group: 1.5 gm continuous infusion for 7 days followed with 1.5 gm po bid

A comparison of day 7/day 8 AUC of MPA indicated that there was not a statistically significant difference between the two AUC when a patient is switched to oral dosing after 7 days of IV infusion. The mean AUC of MPA was comparable for the four treatment groups. The day 7/8 ln (AUC) comparison yielded a ratio of 105 (p=0.538), 110.6 (p=0.538), 104.3 (p=.843) and 90.8% (p=.368) for oral, 1hr IV, 3hr IV and 24 hr continuous IV infusion, respectively. For Cmax, the data on days 1 and 7 follow a trend of Cmax of 1hr IV > Cmax oral> 3 hr IV> Cmax continuous infusion. Day 8 and 14 Cmax are comparable for all the treatment groups except for the continuous infusion group on day 8. There was one patient in the continuous infusion group whose day 8 Cmax (149 μg/mL) and AUC were significantly higher than the rest of the patients; the reason for this was not apparent from the baseline characteristics and demographics. This patient data is included in the analysis. A visual inspection of the mean trough concentrations of MPA between days 2 and 14 (figure 4 on following page) indicate steady state is reached by day 7 (probably sooner) of daily IV infusion.

Figure 4

Mean Pre-Dose. MPA Concentration



Mean AUC(0-12) of MPAG (MPA EQ.)

Day of Treatment	Oral Group	1 hr IV Group	3 hr IV Group	24 cont. IV Grp
	Mean ± SD (n)			
1	383 ± 91.6 (13)	366 ± 98.0 (15)	346 ± 143 (13)	225 ± 52.9 (13)
7	1411 ± 920 (13)	1402 ± 826 (10)	1256 ± 1032 (11)	1642 ± 1353 (14)
8	1353 ± 827 (13)	1444 ± 884 (10)	1396 ± 1274 (10)	1769 ± 1340 (13)
14	1155 (12)	1141 ± 520 (10)	1542 ± 1712 (11)	1502 ± 859 (14)

Oral Group: 1.5 gm MMF po bid.
1 hr IV Group: 1.5 gm bid infused over 1 hr for 7 days followed with 1.5 gm po bid
3 hr IV Group: 1.5 gm bid infused over 3 hr for 7 days followed with 1.5 gm po bid
24 hr IV Group: 1.5 gm continuous infusion for 7 days followed with 1.5 gm po bid

Mean Cmax of MPAG (MPA EQ.)

Day of Treatment	Oral Group	1 hr IV Group	3 hr IV Group	24 cont. IV Grp
	Mean ± SD (n)			
1	45.9 ± 11.1 (13)	43.9 ± 10.6 (15)	44.7 ± 18.3 (13)	35.5 ± 8.98 (13)
7	150 ± 78.5 (13)	149 ± 78.5 (10)	126 ± 86.7 (11)	152 ± 121 (14)
8	140 ± 69.3 (13)	144 ± 76.1 (10)	137 ± 104 (10)	181± 116 (13)
14	124 ± 41.4 (12)	118 ± 46.1 (10)	159 ± 149 (11)	159 ± 72.3 (14)

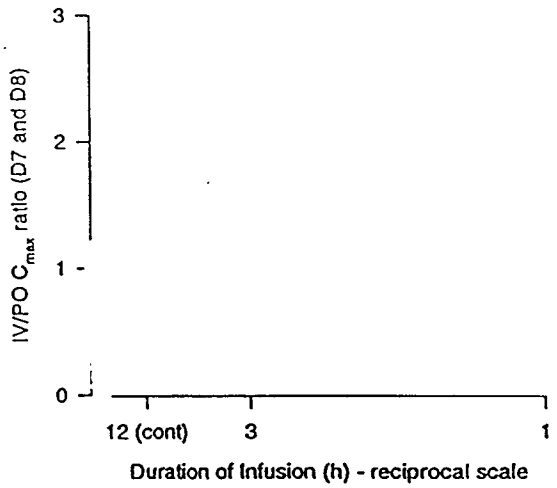
Oral Group: 1.5 gm MMF po bid.
1 hr IV Group: 1.5 gm bid infused over 1 hr for 7 days followed with 1.5 gm po bid
3 hr IV Group: 1.5 gm bid infused over 3 hr for 7 days followed with 1.5 gm po bid
24 hr IV Group: 1.5 gm continuous infusion for 7 days followed with 1.5 gm po bid

There was no statistically significant difference in day 7/8 AUC of MPAG comparisons. The day 7/8 ln (AUC) comparison yielded a ratio of 102.4 (p=0.829), 97.8 (p=.891), 89.5 (p=.559) and 80.4% (p=.136) for the oral, 1hr IV, 3h IV and 24hr continuous infusion groups, respectively. A significant accumulation of MPAG was observed after daily dosing of MMF. This is consistent with what have been experienced with other oral and IV MMF studies and is not expected to be of clinical significance. The relationship of infusion duration with Cmax of MPA was not apparent with Cmax of MPAG. The amount of MPAG excreted in the urine were similar when days 7 and 8 are compared.

Shorter infusion regimens were associated with higher Cmax of MPA. Therefore, using interpolation based on the values obtained for the ratio of day 7 to 8 mean Cmax values an infusion duration of about 2 hours was predicted to provide similar Cmax of MPA when IV MMF administration is followed by the same dose of oral MMF. Thus, a dose of 1gm BID and an infusion of 2 hours duration was selected for the pivotal pharmacokinetic study (MYCS 2734)

Figure # 5

~~Figure 2~~ - C_{max} Ratio IV / PO vs Infusion Duration From Study MYC061



Symbols provide mean values of C_{max} ratio - circles show unedited data line fitted to these values (triangle shows the effect of ignoring the outlier value seen in the in continuous IV infusion group

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Conclusion: The AUC of MPA after IV MMF administration for 7 days were similar to that observed when the patients were switched to a similar dose of oral MMF. Cmax of MPA varied inversely with infusion duration. Visual inspection of predose data indicate steady state conditions were achieved by day 7 (probably sooner) of daily dosing.

Study IID/MYCi2176/USA: Open-Label, Dose Ranging Study of the Safety and Pharmacokinetics of Intravenous Followed by Oral Mycophenolate Mofetil in the Prevention of Acute Rejection in Primary Cadaveric Renal Allograft Recipients (Volume 36 page 1)

Background: MMF (Cellcept) is approved for prevention of organ rejection in renal and cardiac transplant patients. An interim report of this study was originally submitted to NDA 50,722 and reviewed. This is a review of the final report.

Objective: The primary objective was to study the safety and pharmacokinetics of intravenous (IV, infused over 40 mins) mycophenolate mofetil (MMF) administered twice daily (BID) for 7 days at two doses (2 gm/day and 3 gm/day) to patients immediately following primary cadaveric kidney transplantation, followed with MMF 3.0 gm per day (1.5 gm BID) and administered for up to 14 days in patients with delayed graft function (DGF).

Design: This was a phase II open-label, dose-ranging study of IV MMF followed by oral MMF in primary cadaveric renal transplant patients. MMF was administered concomitantly with corticosteriods and cyclosporine. Thirty patients enrolled in the study: 17 received IV MMF 1 gm BID and 13 received IV MMF 1.5 gm BID. Their mean±SD age and weight were 47.1±12.9 yrs and 81.9±20.1 kg, respectively. The first 10 patients enrolled in the study received IV MMF administered at 1 gm BID. Thereafter, patients with immediate graft function (IGF) 6 hours following transplantation received IV MMF at 1.5 gm BID for 7 days except DGF patients who received IV MMF 1 gm BID for 14 days. The duration of the MMF infusion was 40 and 60 mins for the 1 and 1.5 gm doses, respectively. After the IV therapy, patients received oral MMF 1.5 gm BID for the duration of the study; the longest duration of follow-up was 899 days. Pharmacokinetics were assessed on Days 1, 7 and 8 after the 1st dose on each day. Samples for the IV profiles were drawn at 0 (pre-dose), 20, 40 min after infusion began; at the end of infusion; 5, 30 min and 1 and 3 hr after the end of the infusion; and 9 and 12 hr after the infusion began. Samples for the oral profile were drawn at 0 (pre-dose), 1, 2, 4, 8 and 12 hr after the dose was taken. Predose concentrations of MMF were determined on days 2, 3, and 5 following transplantation. Oral pre-dose concentrations for MMF, MPA and MPAG also were determined on days 9, 10, 14, 21 and month 3 following transplantation. The formulation and lot numbers for the IV product were F61443-081 and 30942P135A, respectively and for the oral product the formulation number was F61443-051 and the lot numbers were E2-NF-005 and E3-NF-001.

Data Analysis: The following pharmacokinetic parameters were to be determined for MMF, MPA and MPAG: Cmax, Tmax, Cmin, Cmax/Cmin, AUC(0-12), Cave, Cmax/Cave and fluctuation

Results: There were 21 patients who had evaluable pharmacokinetic data and 30 patients with safety and efficacy summaries. The mean plasma concentration time plot for MMF (the parent compound) is provided in figure 6 on the following page. MMF concentrations were sustained during the infusion but declined rapidly after the infusion was stopped and was not detectable after 5-10 mins post infusion period. MMF was not detected after oral administration.

The pharmacokinetic parameters computed for MMF after IV administration are contained in the following table.

Parameter	Regimen A	Regimen B	Regimen C	Regimen D
	Mean ± SD (n) of MMF			
AUC (μg*hr/mL)#	5.44 ± 2.66 (10)	6.31 ± 2.20 (11)	4.56 ± 5.12 (8)	5.24 ± 3.05 (8)
Cmax (μg/mL)	11.3 ± 4.20 (10)	8.59 ± 2.49 (11)	9.67 ± 10.7 (8)	5.69 ± 4.57 (10)
Tmax (hr)	0.54 ± 0.20 (10)	0.46 ± 0.17 (11)	0.44 ± 0.17 (8)	0.61 ± 0.40 (10)

#AUC (0-12h)
Regimen A: Day 1 of IV dosing with MMF infused over 40 mins at 1gm bid
Regimen B: Day 1 of IV dosing with MMF infused over 60 mins at 1.5 gm bid
Regimen C: Day 7 of IV dosing with MMF infused over 40 mins at 1 gm bid
Regimen D: Day 7 of IV dosing with MMF infused over 60 mins at 1.5 gm bid

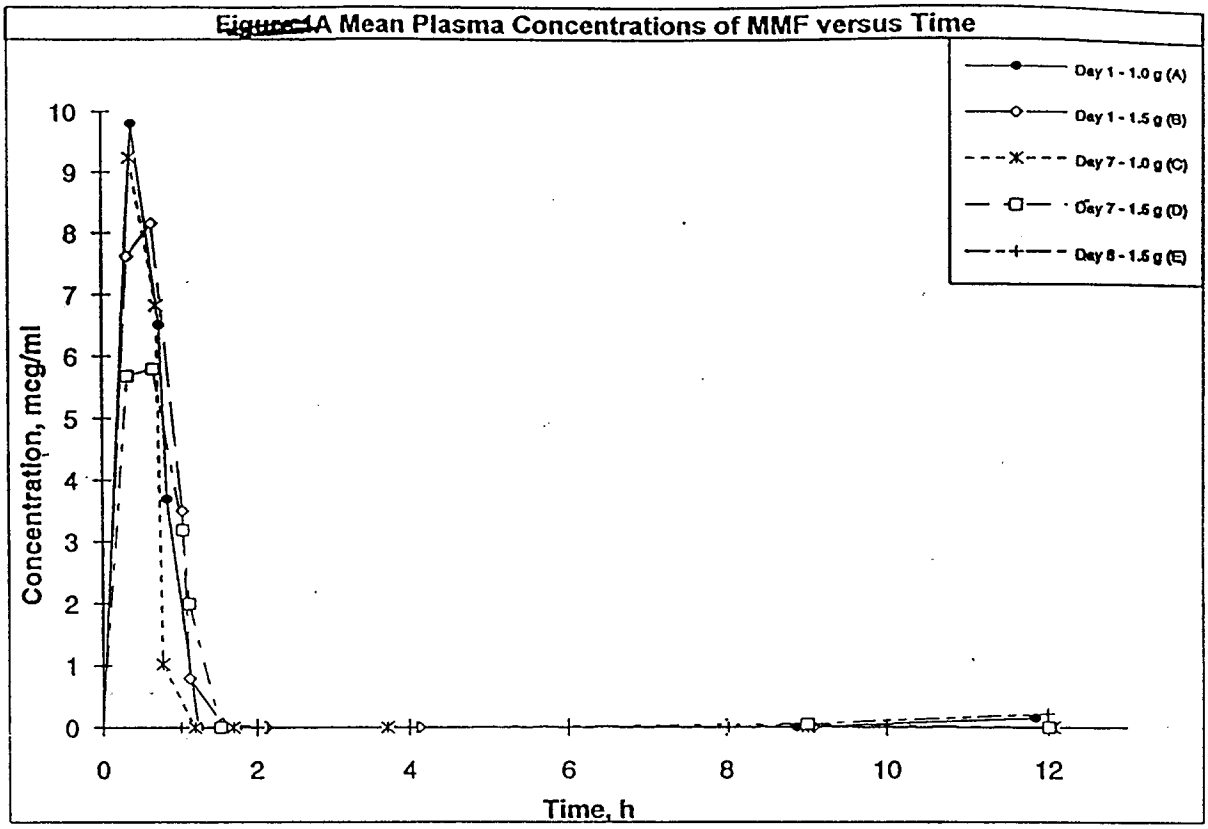
MMF exposure was comparable across treatment regimens. In discussions with the reviewing pharmacologist/toxicologist, the concentration of MMF determined is not expected to be of a safety concern.

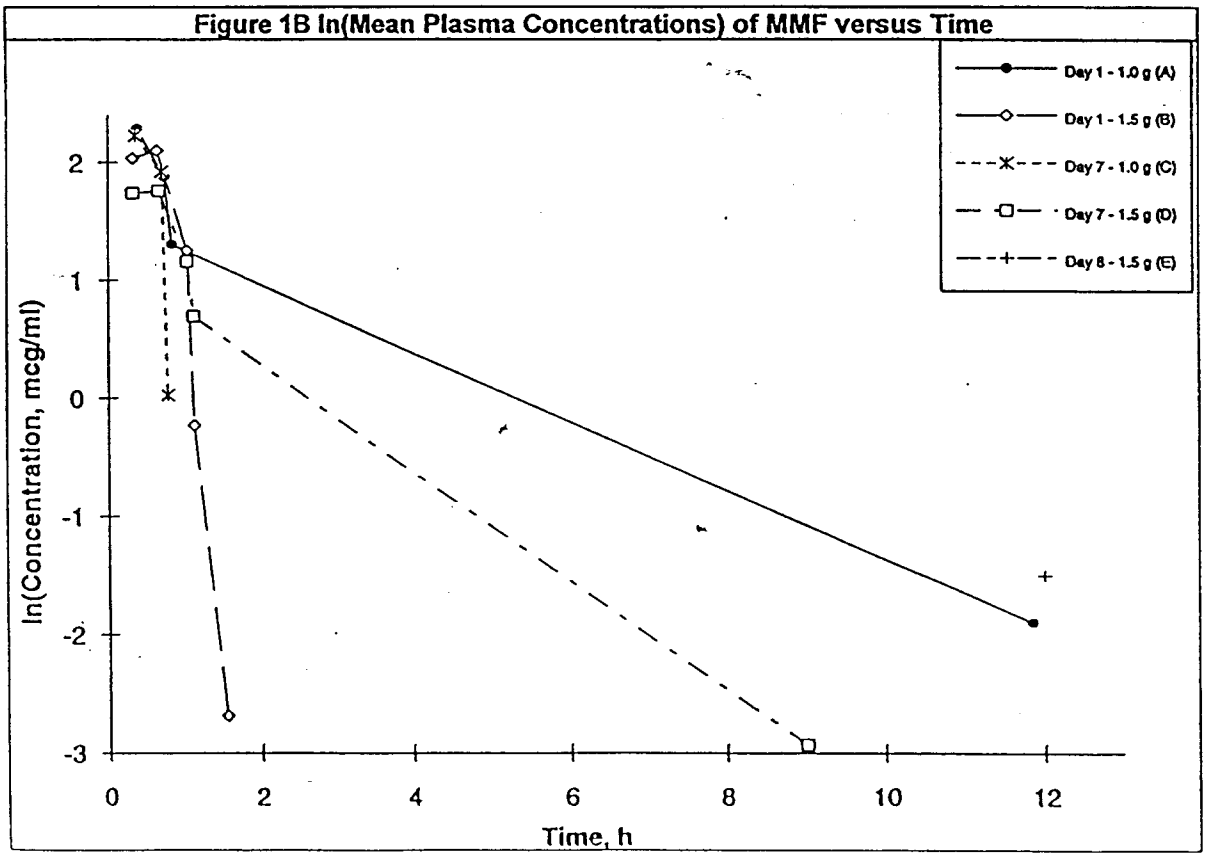
The mean plasma concentration time profile for MPA is provided in the Appendix. Trough concentrations for MPA indicate that overall, steady state conditions appeared to have been achieved by day 7 (probably sooner) of IV dosing (Appendix). As expected, the Cmax after intravenous infusions were higher than that obtained after oral administration. The mean AUC, Cmax and Tmax of MPA are provided in the following table; other computed parameters are contained in the Appendix.

Parameter	Regimen A	Regimen B	Regimen C	Regimen D	Regimen E
	Mean ± SD of MPA (n)				
AUC(μg*hr/mL)#	28.9 ± 23.0 (10)	34.8 ± 9.91 (11)	30.8 ±10.8 (8)	39.1 ± 9.86 (9)	30.3 ± 13.9 (17)
Cmax (hr)	23.6 ± 13.4 (10)	24.8 ± 7.13 (11)	20.0 ± 6.32 (8)	20.9 ± 6.35 (10)	7.95 ± 4.91 (17)
Tmax (hr)	0.68 ± 0.15(10)	0.83 ± 0.29 (11)	0.67 ± 0.14 (8)	0.94 ± 0.23 (10)	1.53 ± 1.07 (17)

#AUC (0-12h)
Regimen A: Day 1 of IV dosing with MMF infused over 40 mins at 1gm bid
Regimen B: Day 1 of IV dosing with MMF infused over 60 mins at 1.5 gm bid
Regimen C: Day 7 of IV dosing with MMF infused over 40 mins at 1 gm bid
Regimen D: Day 7 of IV dosing with MMF infused over 60 mins at 1.5 gm bid
Regimen E: Day 8- First day of oral dosing 1.5 gm with MMF after 7 days of IV dosing

Figure 6





There was considerable variation about the mean for AUC. There was no statistically significant difference in AUCs for the five treatment groups. However, an evaluation of the individual patient data indicate that day 7 AUC of MPA was about 50% higher after IV infusion of MMF 1.5 gm compared to day 8 AUC after oral administration of 1.5gm MMF. However, day 7 mean AUC of MPA after IV infusion of MMF 1 gm was similar to day 8 AUC after oral administration of 1.5 gm MMF. There were 4 patients who had an increase in AUC ranging from while in 3 patients there were decreases ranging from about

There was a tendency towards an increase in mean AUC with an increase in dose; however, the mean increase in AUC was not proportional to dose. Multiple dosing for 7 days of IV MMF did not result in significant accumulation of MPA (based on day 1 and day 7 AUC comparisons).

The mean plasma concentration time profiles for MPAG after IV and oral administration of MMF are provided in Appendix. Day 7 concentrations of MPAG were significantly higher than that observed on day 1. The following table contains AUC, Cmax and Tmax of MPAG after administration of MMF; other computed parameters are in the Appendix.

Parameter	Regimen A	Regimen B	Regimen C	Regimen D	Regimen E
	Mean ± SD of MPA (n)				
AUC(μg*hr/mL)#	253± 50.3 (10)	380 ± 163 (11)	1088 ±439 (8)	1253 ± 774 (9)	1155 ± 641 (17)
Cmax (hr)	32.3 ±5.80 (10)	54 ± 18 (11)	110 ± 35.9 (8)	134 ± 66.4 (10)	114 ± 52.9 (17)
Tmax (hr)	1.26 ± 0.33 (10)	2.51 ± 3.16 (11)	1.53 ± 0.94 (8)	1.49 ± 0.30 (10)	4.47 ± 3.18 (17)

#AUC (0-12h)

Regimen A: Day 1 of IV dosing with MMF infused over 40 mins at 1gm bid
Regimen B: Day 1 of IV dosing with MMF infused over 60 mins at 1.5 gm bid
Regimen C: Day 7 of IV dosing with MMF infused over 40 mins at 1 gm bid
Regimen D: Day 7 of IV dosing with MMF infused over 60 mins at 1.5 gm bid
Regimen E: Day 8- First day of oral dosing 1.5 gm with MMF after 7 days of IV dosing

There was significant accumulation of MPAG after multiple dosing of intravenous MMF for 7 days. Day 7 MPAG after IV dosing of MMF 1 gm and 1.5 gm bid were similar to that observed after oral dosing. MPAG levels have not been associated with any adverse effect, hence, should not be of clinical significance.

Conclusion: Administration of IV MMF provided no statistically significant difference in AUC of MPA to that observed after oral administration. However, there was a trend towards higher exposure from infusing 1.5 gm of MMF than administering 1.5 gm orally. Unlike oral administration, the parent compound (MMF) was detected during the IV infusion but concentrations declined rapidly after the infusion was stopped. Steady state conditions appeared to have been reached by day 7 (probably sooner) of IV dosing. The applicant reported that the only adverse events clearly related to IV administration were infusion site reactions. Intravenous MMF provided at least a similar degree of exposure of MPA as oral MMF and appears to be a logical alternative to oral administration during the first 7 days after transplantation.

Pharmacokinetics in Healthy Volunteers

Study CPP/MYC 2294 (Cl 6778): An Evaluation of the Pharmacokinetics and Bioavailability of Mycophenolate Mofetil Following a 1.5 g Intravenous and Oral Dose in Healthy Volunteers (Volume 30 page 1)

Background: This study was submitted and reviewed under NDA 50,722 by Dr. Chandra Sahajwalla. A summary of the discussion of the results of his review is presented in this overview. For a complete discussion of the study, please refer to the original review.

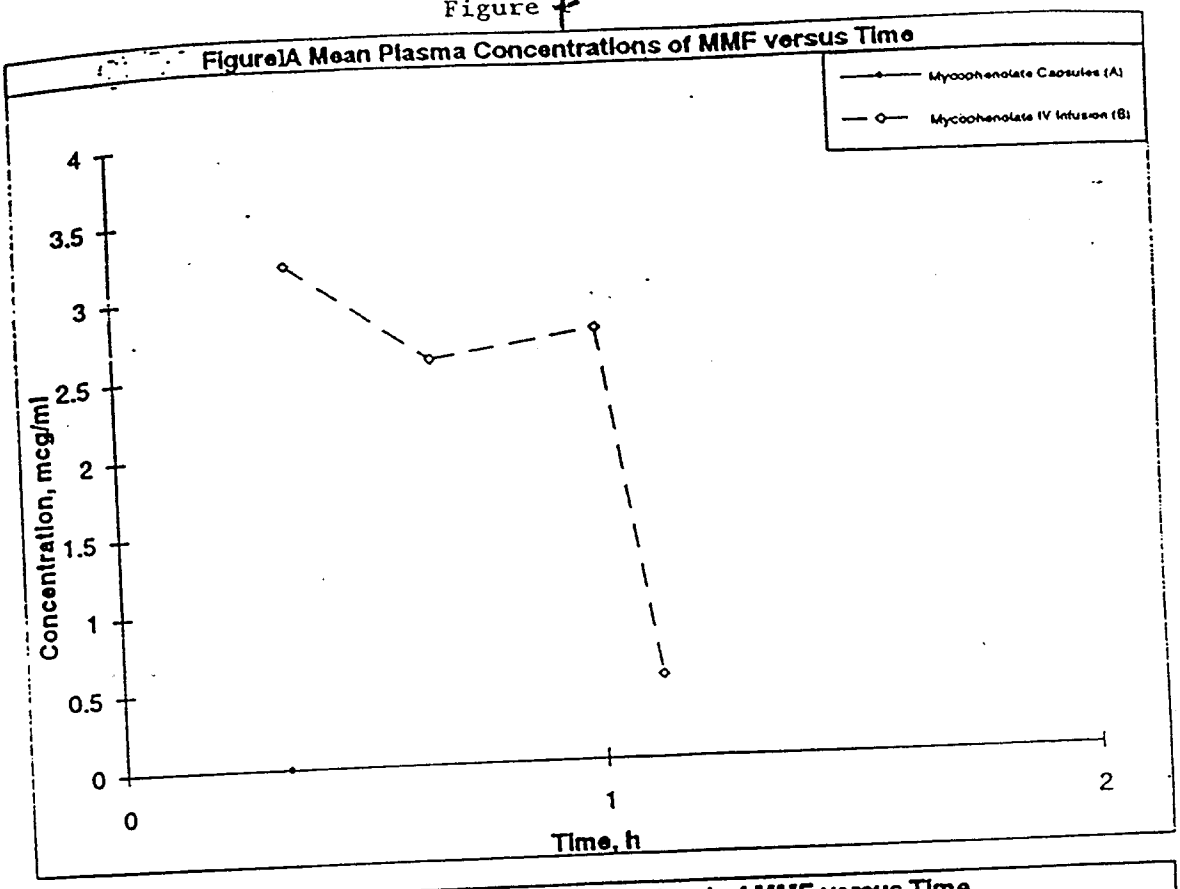
Objectives: To evaluate the bioavailability of 1.5 gm of mycophenolate mofetil (MMF), a prodrug of mycophenolic acid (MPA) based on the total AUC of MPA and its glucuronide conjugate (MPAG) when administered as a single oral dose (in capsules) versus when infused intravenously (IV) over 60 minutes to the same subjects. The secondary purpose was to quantitate the urinary metabolites of MMF (MPA and MPAG) following these IV and oral doses of MMF.

Design: This was an open-label, randomized, two-period, single-dose crossover study in 12 healthy subjects. Blood and urine samples were collected up to 48 hours. Refer to original review under NDA 50,722 for details of the design.

Results and Conclusion: The mean plasma MMF concentration time profile after IV administration is presented in figure 7 on the following page. MMF was below the quantitation limit (BQL) 20 mins (first sampling time) after oral administration. However, MMF was measurable in plasma 20 minutes after initiation of IV infusion but declined rapidly after the infusion. MMF was detectable in plasma at 5 minutes but was BQL at 10 minutes after completion of the IV infusion. In discussions with the pharmacology reviewer, the extent of exposure to MMF (AUClast = 0.73 μg*hr/mL) after IV administration is not expected to be of a safety concern.

Parameter	MPA		MPAG (MPA Equivalents)	
	IV	Oral	IV	Oral
	Mean ± SD (n=12)			
Tmax (hr)	1.03 ± 0.04	0.99 ± 0.41	1.65 ± 0.28	1.81 ± 0.47
Cmax (μg/mL)	47.2 ± 9.33	34.0 ± 7.09	39.3 ± 9.11	43.1 ± 6.75
T ½ (hr)	16.6 ± 5.83	17.9 ± 89.8	21.8 ± 19.0	16.1 ± 5.15
AUC(last) (μg*hr/mL)	99.6 ± 24.4	89.8 ± 17.8	340 ± 91.9	411 ± 105
Total AUC (μg*hr/mL)	108 ± 26.0	101 ± 23.4	442 ± 102	480 ± 105
RS Excreted (%)	0.268 ± 0.297	0.486 ± 0.475	72.1 ± 6.65	71.3 ± 6.77
F (%)	100	94.1 ± 16.2	100	112 ± 25.4

Figure 7



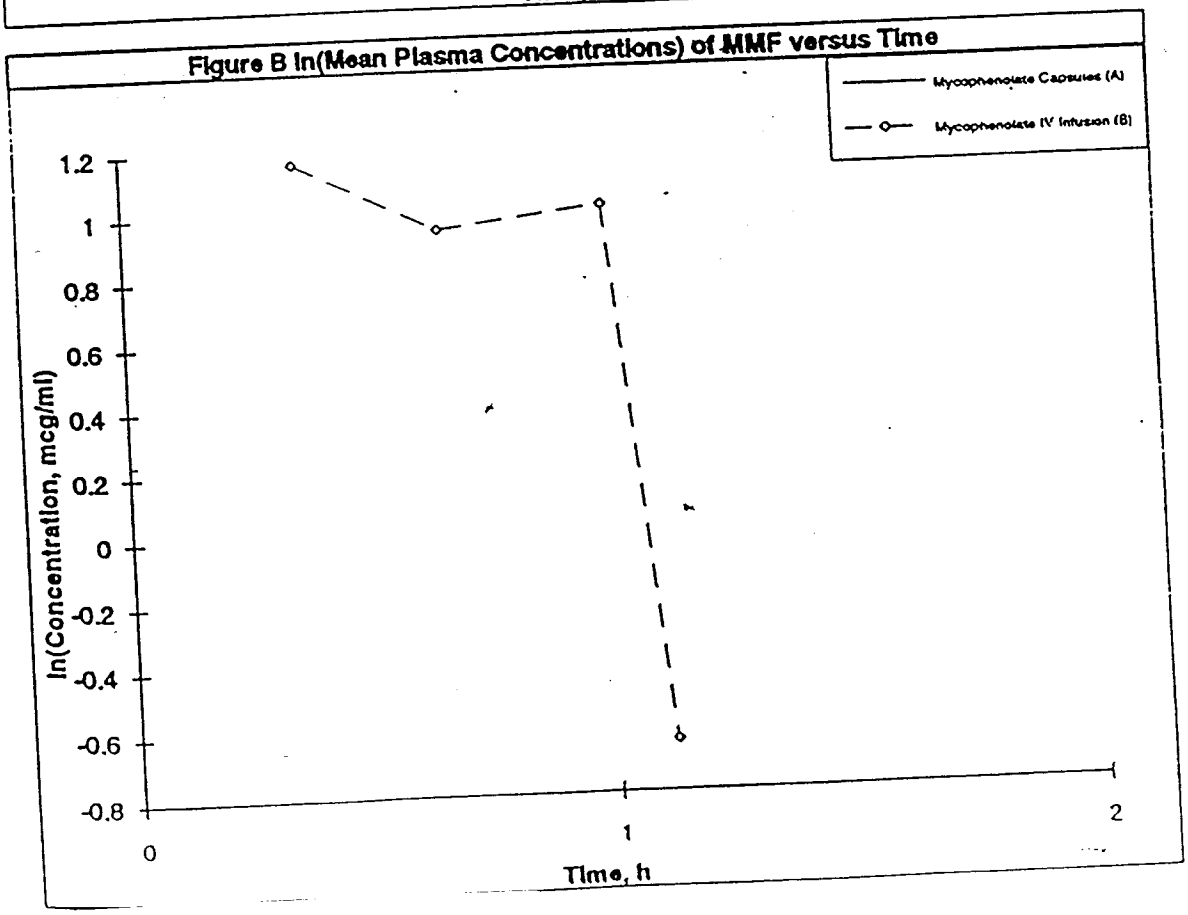


Table 4

Mean MMF Plasma Concentrations (mcg/ml) and Computed Parameter Summary

Nominal Time		Regimen A			Regimen B			p-values from ANOVA		
	(h)	Mean	Std Dev	N	Mean	Std Dev	N	Regimen	Period	Sequence
	0.00			0	0.	0.	12			
	0.33	0.	0.	12	3.20	1.38	12	<0.001	0.796	0.796
	0.67			0	2.58	1.05	12			0.660
	1.00			0	2.74	1.64	12			0.341
	1.08				0.524	0.434	12			0.263
	1.17				0.	0.	12			
	1.25			0						
	1.50			0	0.	0.	12			
	2.00			0			0			
	3.00			0			0			
	4.00			0			0			
	6.00			0			0			
	8.00			0			0			
	10.00			0			0			
	12.00			0			0			
	16.00			0			0			
	24.00			0			0			
	36.00			0			0			
	48.00			0			0			
Parameter										
AUClast	(mcg*h/ml)	NC	NC	0	2.35	0.725	12			0.929
Cmax	(mcg/ml)	NC	NC	0	3.47	1.48	12			0.821
ln(AUClast)		NC	NC	0	0.808	0.314	12			0.913
ln(Cmax)		NC	NC	0	1.16	0.425	12			0.813
Tmax	(h)	NC	NC	0	0.643	0.328	12			0.041

Note: Values below the limit of quantitation (.400 mcg/ml) are treated as zero in statistical calculations.
NC= Not Computed
Regimens:
A = Mycophenolate mofetil 250 mg x 6 capsules.
B = Mycophenolate mofetil 1.5 g infusion over 60 minutes.

The mean absolute bioavailability (based on MPA total AUC) of oral MMF was 94%, indicating almost complete absorption. The mean MPA Cmax following oral MMF was 28% lower than that following IV MMF infused over 60 mins. In the urine, the major metabolite (MPAG) accounted for 72.1 and 71.3% of the IV and oral MMF doses, respectively.

Dr. Sahajwalla concluded in his review that MMF had essentially complete absorption after oral administration and most of the drug was excreted as MPAG. The amount of MPAG excreted after IV infusion is similar to that after oral administration. This reviewer agrees with the conclusions of the previous review.

Study ICM/MYCx 1900/USA: A Pharmacokinetic and Safety Study of Intravenous Mycophenolate Mofetil Administered in Ascending Doses Separated by Washout Periods in Normal Volunteer Subjects (Volume 29 page 1)

Introduction: This study was originally submitted and reviewed under NDA 50,722. This is a brief summary of the review; refer to the original review for details.

Objective: To evaluate the pharmacokinetics and safety of an intravenous formulation of mycophenolate mofetil (MMF) in normal volunteers

Design: This was a randomized, double-blind, five-period, ascending single dose study. Six male subjects (mean age and weight were 32 years and 87.2 kg, respectively) enrolled and completed the study. Each subject received a dose of placebo (P) and four ascending doses of MMF (A, B, C and D). There was a 7 day washout period between doses. Intravenous (IV) doses of placebo (0), 1.5, 7.5, 15.0 and 22.5 mg MMF per kg of body weight were infused over 1 hour. Serial blood samples were collected up to 48 hours after the start of infusion. Plasma concentrations of MMF, mycophenolic acid (MPA) and mycophenolic glucuronide conjugate (MPAG) were determined. Urine was also collected for 0 to 48 hour intervals.

Results: MMF, MPA and MPAG were all detected in plasma at 5 minutes, the first sampling point following the start of infusion. MMF concentrations seen at 5 minutes were similar to the levels observed at 20, 40 and 60 minutes. By 30 mins after the end of infusion, MMF was not detectable in the plasma. The following tables summarize the mean pharmacokinetic parameters

Pharmacokinetic Parameters for MMF

Parameter[a]	1.5 mg/kg (A)	7.5 mg/kg (B)	15.0 mg/kg ©	22.5 mg/kg (D)
	Mean ± SD (n=6)			
Tmax (hr)	0.550 ± 0.343	0.686 ± 0.386	0.319 ± 0.355	0.467 ± 0.321
Cmax (hr)	0.783 ± 0.235	2.48 ± 1.43	4.93 ± 1.82	6.64 ± 2.24
AUClast (μg*hr/mL)	0.524 ± 0.320	2.01 ± 1.20	3.96 ± 1.49	5.52 ± 2.19

[a] Half-life and total AUC could not be calculated because of inadequate plasma concentrations (BQL at first postinfusion time)

Pharmacokinetic Parameters for MPA

Parameter[a]	1.5 mg/kg (A)	7.5 mg/kg (B)	15.0 mg/kg ©	22.5 mg/kg (D)
	Mean ± SD (n=6)			
Tmax (hr)	1.00 ± 0.007	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Cmax (hr)	2.51 ± 0.235	15.8 ± 1.82	35.3 ± 4.79	60.2 ± 7.20
T ½ (hr)	---[b]	15.2 ± 13.2	12.6 ± 5.11	14.7 ± 3.69
AUClast (μg*hr/mL)	4.21 ± 0.802	30.8 ± 5.28	67.3 ± 7.31	116 ± 14.8
Total AUC (μg*hr/mL)	---[b]	34.1 ± 5.37	70.8 ± 7.13	121 ± 14.

[b] Mean not reported since last measurable MPA concentration was at 16 hours

Pharmacokinetic Parameters for MPAG

Parameter	1.5 mg/kg (A)	7.5 mg/kg (B)	15.0 mg/kg ©	22.5 mg/kg (D)
	Mean ± SD MPAG (n=6)			
Tmax (hr)	1.51 ± 0.02	1.50 ± 0.007	1.50 ± 0.00	1.67 ± 0.267
Cmax (μg/mL)	2.33 ±0.60	13.1± 3.59	28.0 ± 9.12	41.6 ± 9.93
T ½ (hr)	14.3 ± 8.48	14.9 ± 11.3	13.1 ± 4.27	13.8 ± 3.48
AUC last (μg*hr/mL)	19.7 ± 8.09	112 ± 25.0	238 ± 50.6	352 ± 80.5
Total AUC (μg*hr/mL)	27.5 ± 12.0	123 ± 26.3	256 ± 46.6	377 ± 76.9

MPA and MPAG half-lives were similar at all dose levels (except MPA half-life could not be calculated for the 1.5 mg/kg dose level). Mean values of AUC(total) of MPA and MPAG appear to increase in a dose proportional manner.

Following administration of the 1.5, 7.5, 15.0 and 22.5 mg/kg dose levels, 0.00, 0.110, 0.207 and 0.31% respectively, of the administered MMF was excreted in urine as MPA, whereas 15.8, 68.2, 61.8 and 60.8% of the administered dose was excreted in the urine as MPAG.

Conclusion: The previous reviewer of this study concluded that MPA was formed rapidly after the start of IV administration of MMF. The mean values of Cmax and total AUC of MPA and MPAG appeared to increase approximately proportionally with dose. MPA and MPAG half-life values did not change with the MMF dose administered. This reviewer agrees with the conclusions from the previous review of this study.

Pharmacokinetics in Special Populations

Study CPP/MYCc2118/USA (Cl 6790): A Single Dose Pharmacokinetic Study of Mycophenolate Mofetil in Subjects with Normal Renal Function and in Patients with Varying Degrees of Renal Function, Including Dialysis Patients (Volume 33 page 1)

Background: The final report of this study was originally submitted to NDA 50,722. It was reviewed under that application. This is a brief summary of that review.

Objectives: To evaluate the pharmacokinetics of mycophenolate mofetil (MMF) administered orally as a single 1-g dose in normal subjects and in patients with varying degrees of renal function, including patients undergoing dialysis. The secondary objectives of the study were to evaluate the dialysis clearance of mycophenolic acid (MPA) and its glucuronide (MPAG) and to evaluate the pharmacokinetics of single IV dose of MMF in the moderate to severe renal impairment patient group.

Design: A single center, open-label, single dose, parallel design study in healthy subjects and patients with varying degrees of renal impairment, includine patients undergoing dialysis. Group I, II, and III had GFR >80 respectively. Group IVA (not on dialysis) had GFR < 25 mL/min/1.73 m^2 and Group IVB had GFR < 25 mL/min/1.73 m^2 (on cyclosporine and not on dialysis). Group V had GFR < 25 mL/min/1.73 m^2 and on dialysis. Group V patients (dialysis group) received an oral dose of MMF twice (during an interdialytic period, Group VA; and just prior to hemodialysis, Group VB), following a washout period of 2 weeks between each dose, Group IV (A and B) also received a single IV dose of MMF following a 2 week washout period after oral dosing. Refer to original review for details of the design. All subjects/patients oral dose of 1 gm of MMF except group V. Group IV patient also received a single 1 gm IV dose following a 2 week washout period after oral dose.

Results: Mean MPA and MPAG parameters are presented in the table on the following page. MPA Cmax were statistically significantly different among the different renal function groups. A trend towards an increase in AUClast of MPA was observed with increasing renal impairment. A significant amount of MPAG was observed in the severe renal impairment groups as compared to the healthy subject group. The amount excreted as MPAG decreased with increasing renal impairment. Dialysis did not affect MPA and MPAG pharmacokinetics. Administration of MMF with and without cyclosporine did not affect the pharmacokinetics of MPA or MPAG. Administration of IV and oral MMF to groups IVA and IVB resulted in similar plasma profiles except for Cmax of MPA.

Conclusion: Cmax of MPA was significantly different and considerable accumulation of MPAG was observed with an increase in renal impairment. MPA and MPAG pharmacokinetics were not altered by dialysis, In the moderate to severe renal impairment group, the AUClast of MPA and MPAG were similar following IV and oral dosing of MMF suggesting complete abosrption of MMF. This reviewer agrees with the above conclusions from the previous review.

Study CPP/MYCs030/GER (CL 6812): Investigation of Mycophenolate Mofetil Pharmacokinetics Following an Intravenous Infusion of a 1 gm Dose to Volunteers with Severe Hepatic Impairment (Volume 31 page 1)

Background: The final report of this study was submitted to NDA 50,722 and reviewed under that application. The current report is a brief overview of that review and the reader is referred to NDA 50,722 for details.

Objectives: To evaluate the effect of severe hepatic impairment on the pharmacokinetics of mycophenolate mofetil (MMF), mycophenolic acid (MPA) and its glucuronide (MPAG) following an intravenous infusion.

Design: This was open label, single dose study in 6 hepatically impaired volunteers between the ages of 18 to 65 years with aminopyrine breath test of less than 0.2% of dose exhaled in 30 minutes. All subjects had a diagnosis of hepatic impairment resulting from alcoholic cirrhosis. Single IV dose of 1 gm given as a 40 minute infusion (6 mg/mL in 5% dextrose solution) was administered. Plasma samples were collected during and up to 96 hours after the start of infusion. Urine samples were collected up to 96 hours following the start of infusion.

Results: The mean pharmacokinetic parameters are summarized in the following table.

Parameter	MMF	MPA	MPAG
	Mean ± SD		
AUClast (μg*hr/mL)	1.64 ± 0.642	44.1 ± 15.5	185 ± 45.6
Clearance (L/min)	NC	NC	0.066 ± 0.022
Cmax (μg/mL)	3.25 ± 1.24	39.0 ± 10.6	28.1 ± 6.89
Half-Life (hr)	NC	NC	5.49 ± 3.73
RS Excreted (%)	NC	1.35 ± 1.35	64.7 ± 61.1
Clr (0-96)(L/h)	NC	0.254 ± 0.303	2.45 ± 1.69

NC = not calculated

Conclusion: MMF was detected in plasma during the infusion; however, it was not detected 5 mins after the infusion was terminated suggesting a rapid conversion to MPA. Therefore, patients with severe alcoholic cirrhosis rapidly metabolized IV MMF to MPA. All MPA was cleared within 12 hours following dosing. A high proportion MMF was excreted in the urine as MPAG. This reviewer agrees with the conclusion made in the original review of this study under NDA 50,722.

SUMMARY TABLE

Parameter (Mean ± SD)

MPA

	Group I (N = 6)	Group II (N = 6)	Group III (N = 6)	Group IV (PO) (N = 7)	Group VA (N = 6)	Group VB (N = 6)
T_{max} (hr)	0.750 (0.274)	0.750 (0.274)	0.750 (0.274)	1.00 (0.408)	0.750 (0.274)	2.33 (3.78)
C_{max} (µg/mL)*	25.3 (7.99)	26.0 (3.82)	19.0 (13.2)	16.3 (10.8)	16.1 (7.26)	7.07 (2.78)
AUC_{last} (µg·hr/mL)	45.0 (22.6)	59.9 (12.9)	52.9 (25.5)	78.6 (46.4)	76.9 (25.4)	60.5 (38.1)
RS Excreted (%)	0.287 (0.334)	0.039 (0.049)	0.601 (0.814)	0.120 (0.224)	0.133 (0.251)	0.203 (0.441)

MPAG (MPA EQ.)

T_{max} (hr)	1.42 (0.206)	1.58 (0.204)	4.00 (5.89)	2.43 (1.69)	3.00 (2.51)	2.17 (0.516)
C_{max} (µg/mL)	27.9 (6.01)	30.5 (6.79)	27.3 (8.93)	32.0 (10.6)	37.8 (13.9)	32.6 (11.2)
AUC_{last} (µg·hr/mL)*	287 (47.0)	426 (21.4)	795 (228)	1411 (608)	1830 (718)	1548 (659)
RS Excreted (%)*	72.0 (14.5)	71.8 (5.62)	59.1 (16.5)	42.8 (23.3)	10.2 (18.2)	5.20 (8.43)

Group IV (IV) (N = 4)	MMF	MPA	MPAG (MPA Eq.)
T_{max} (hr)	0.550 (0.195)	0.717 (0.031)	2.05 (1.45)
C_{max} (µg/mL)	6.10 (1.50)	26.5 (7.70)	33.4 (9.25)
AUC_{last} (µg·hr/mL)	3.12 (0.811)	62.4 (19.3)	1327 (372)

* $p < 0.05$

Figure 8: Comparison of Individual Healthy Subject and Renal Transplant Patient Data for MPA AUC Following IV and PO MMF Administration